Neurosci Bull October 1, 2009, 25(5): 237-266. http://www.neurosci.cn
DOI: 10.1007/s12264-009-0905-4

·Review·

Roles of the hippocampal formation in pain information processing

Ming-Gang LIU[1], Jun CHEN[1,2]

[1]*Institute for Biomedical Sciences of Pain, Capital Medical University, Beijing 100069, China*
[2]*Institute for Biomedical Sciences of Pain and Institute for Functional Brain Disorders, Tangdu Hospital, The Fourth Military Medical University, Xi'an 710038, China*

Abstract: Pain is a complex experience consisting of sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. Now it has been gradually known that noxious information is processed by a widely-distributed, hierarchically-interconnected neural network, referred to as neuromatrix, in the brain. Thus, identifying the multiple neural networks subserving these functional aspects and harnessing this knowledge to manipulate the pain response in new and beneficial ways are challenging tasks. Albeit with elaborate research efforts on the cortical responses to painful stimuli or clinical pain, involvement of the hippocampal formation (HF) in pain is still a matter of controversy. Here, we integrate previous animal and human studies from the viewpoint of HF and pain, sequentially representing anatomical, behavioral, electrophysiological, molecular/biochemical and functional imaging evidence supporting the role of HF in pain processing. At last, we further expound on the relationship between pain and memory and present some unresolved issues.

Keywords: pain; hippocampal formation; anatomy; behavior; electrophysiology; functional imaging

1 Introduction

It has been now widely accepted that pain is a complex phenomenon resulting from a three-dimensional integration of sensory-discriminative, affective-motivational and cognitive-evaluative axes [1,2]. In addition, it is currently believed that the lateral pain system is more involved in sensory-discriminative aspects of pain processing, subserving the ability to analyze location, intensity and duration of the stimulus, whereas the medial system is more responsible for processing the affective-motivational component, giving rise to the unpleasant character of pain perception [3-5]. The cognition axis is probably associated with higher brain centers, accounting for attention, anticipation and memory of past experiences. Therefore, the understanding of pain as a multidimensional experience suggests that the inherent characteristics of pain experience are likely to be reflected in a matrix of widely distributed and hierarchically interconnected neural network in the brain [3,6,7].

There is now a consensus of idea that pain, when becomes persistent or chronic, may cause not only sensory dysfunction (spontaneous pain, hyperalgesia and allodynia) but also various functional brain disorders, such as anxiety, amnesia, insomnia and depression [8-11]. These co-morbidities of chronic pain make it necessary to extend the pain research from lower levels of the 'pain matrix' into the higher level of cortical and subcortical brain structures [7,12]. In fact, a growing number of studies have been performed on both animals and human subjects, using a myriad of experimental tools and techniques, to examine pain-related changes in the brain. Unfortunately, albeit with the elaborate research ef-

Corresponding Author: Jun CHEN
Tel: +86-29-84777942/10-83911513; Fax: +86-29-84777945/10-83911491
E-mail: junchen@fmmu.edu.cn; chenjun@ccmu.edu.cn;
Article ID: 1673-7067(2009)05-0237-30
CLC number: Q432; R338.3
Document code: A
Received date: 2009-09-05

forts exerted on the cortical responses to painful stimuli or clinical pain [13-16], the limbic system has received the least attention.

The hippocampal formation (HF), an integral component of the limbic system [17-18], has long been implicated in several functions such as arousal and attention [19], learning and memory [20-23], emotion and affect [24,25], sensory motor integration [17,26] and so on. However, cumulating efforts from many laboratories over the past years have allowed the more clear dissection of the roles of HF in pain processing. Indeed, there have been substantial behavioral, electrophysiological, molecular/biochemical and functional imaging evidence supporting the putative relationship between the HF and affective/motivational component of pain perception [12,27-36]. Melzack and Casey[1] proposed that the limbic forebrain structures, including the HF, play important roles in the 'aversive drive and affect that comprise the motivational dimension of pain'. Here, we review previous studies regarding the involvement of HF in pain perception, presenting various aspects of evidence for an association between the hippocampus and pain.

2 Anatomy of the HF related to pain

2.1 A brief overview The HF is a bilaterally symmetrical structure that is situated in the caudal part of the brain, comprising the hippocampus proper (consisting of CA3, CA2, and CA1), dentate gyrus (DG) and subiculum [17,37,38]. Both hippocampal and DG fields are folded into a shape reminiscent of the letter "C". Generally, the HF appears as an elongated structure with its long axis ranging from the septal nuclei rostrodorsally to the incipient temporal lobe caudoventrally. The long axis is generally referred to as the septotemporal axis and the orthogonal axis referred to as the transverse axis [39,40]. The cortex that forms the HF mainly has a three-layered appearance. The first layer is a deep layer, comprising a mixture of afferent/efferent fibers, basal dendrites of the cell layer and interneurons. In the DG this layer is called the hilus, whereas in the CA regions it is referred to as the stratum oriens. Superficial to this polymorph layer is the cell layer, which is composed of principal cells and interneurons. In the DG this layer is called the granule layer, whereas in the CA regions and the subiculum it is referred to as the pyramidal cell layer (stratum pyramidale). The most superficial layer is referred to as the molecular layer (the stratum moleculare) in the DG and the subiculum. In the CA region the molecular layer is subdivided into a number of sublayers. In CA3, three sublayers are distinguished: the stratum lucidum, which receives input from the DG (mossy fiber); the stratum radiatum, comprising the apical dendrites of the neurons located in the stratum pyramidale; and, most superficially, the stratum lacunosum-moleculare, comprising the apical tufts of the apical dendrites and connecting with the perforant path. The lamination in CA2 and CA1 is similar, with the exception that the stratum lucidum is missing[37,38]. For an extensive description of the hippocampal structure and cytoarchitecture, please refer to the following original books and reviews, which is beyond the scope of the present paper[17,39,40].

2.2 Afferents to the HF Neuronal tracing studies have revealed an enormous complexity of the afferent and efferent connection of the HF. However, it is not the intention of this article to present a detailed review of these neuroanatomical studies. Conversely, only those anatomical connections associated with pain ascending systems are briefly outlined. It is really a formidable and contentious issue how the peripheral noxious information is conveyed to the HF. Presumably, we suppose two major pathways associated with painful information entry into the hippocampus that will be discussed below.

2.2.1 Entorhinal cortex as a main station relaying pain signals to the HF On the basis of neuroanatomical studies, the entorhinal cortex (EC), an elementary part of the parahippocampal area in lower species and the parahippocampal gyrus in primates or humans, has long been regarded as a relay station that provides the major source of afferent input to the hippocampus[38,41,42]. According to standard views, sensory information mainly enters the hippocampus via two inputs from the EC, the so-called perforant path. The first input comprises the axons of layer II EC neurons that terminate on the dendrites of the DG. This input is then processed serially via the traditional trisynaptic pathway[43-45]. The second input comprises the axons of layer III EC neurons that

terminate directly on the distal dendrites of CA1 and subiculum[46,47]. This bundle of axons is accompanied by a projection from layer II EC neurons to CA3 neurons[48-50]. Together with the EC-CA1 pathway, this cortico–hippocampal input is often called the temporoammonic path. The two separate branches of the perforant path projection to the HF have also been corroborated by electrophysiological studies[51-55]. In addition, there is a prominent and topologically arranged circuitry between the EC and the HF (for details, see[38]). Of the two EC inputs, the trisynaptic pathway has long been assumed as the major route by which cortical information reaches the HF. However, mounting evidence have pointed towards to the importance of the direct pathway, i.e. the temporoammonic path, in determining hippocampal function[41,53] Then what is the relationship between the two perforant path pathways to pain? Given the electrophysiological results from Khanna's group[56-58], it might be logically predicted that formalin-induced pyramidal cell excitation is dependent on the excitatory input from the EC, implicating a possible link between EC and pain processing in the HF (see below). Nonetheless, the exact route by which peripheral noxious information enters the HF via the EC is still unclear, but here we try to propose two possibilities.

2.2.1.1 The Papez circuit In 1937, Papez proposed the well-known 'Papez circuit', including the hypothalamus (mammillary bodies), anterior thalamic nuclei, cingulate cortex, and the hippocampus, which he believes contributes a harmonious mechanism responsible for the expression of central emotion[18]. From this circuit, one may feel not difficult to find a reciprocal connection between some pain-related regions with the HF, such as the anterior cingulate cortex (ACC). Indeed, there are reports showing that the ACC projects fibers to the subiculum of the HF and the EC[59]. Furthermore, the cingulum bundle, one part of the 'Papez circuit', contains fibers that project from the anterior thalamic nuclei to the ACC and HF[60] as well as fibers from the frontal cortex to the hippocampus and cingulate cortex[61]. Using evoked potentials, Foltz and White[62] demonstrated that the cingulum bundle connects the medial frontal cortex, anterior thalamic nuclei, and the rostra1 midline and intralaminar nuclei with the HF through the EC. Taken these descriptions together, it seems not unreasonable to speculate that peripheral-ascended painful information may gain access to the HF via other pain-related brain areas, such as the thalamus and ACC, through a route similar to the 'Papez circuit', of which the cingulum bundle and EC may play fundamental roles. As supportive evidence, Vaccarino and Melzack[63] found that microinjection of lidocaine into the cingulum bundle, either pre- or post-treatment, resulted in a time-dependent analgesia in the formalin test (see below).

2.2.1.2 Cortico-limbic pathway It is well known that the EC receives massive synaptic input from neocortical association areas and also less pronounced input from primary sensory areas. In addition, it receives input from many subcortical regions, including the midbrain raphe nuclei, the ventral tegmental area, the locus coeruleus, and so on[41]. Interestingly, a cortico-limbic pathway has been described to pass from the primary and secondary somatosensory cortices to insular and parietal cortical structures, then to the amygdala, the perirhinal cortex and the hippocampus, and ultimately converges on the same structures that are directly activated by the spinothalamic pathways[64,65]. This pathway integrates sensory pain characteristics with information from other sensory systems as well as learning and memory, thus adding a cognitive aspect regarding long-term consequences to affective pain processing[66,67]. According to this cortico-limbic pathway, an indirect route for pain signals into the HF is naturally expected: the interaction or crosstalk between the lateral and medial system[66]. To note, the insula is one critical region in this cortico-limbic pathway and the efferents from the insula supply the HF via its projection to the parahippocampal region, among which is the EC[64,65].

2.2.2 Septo-hippocampal pathway An alternative pathway conveying painful information to the HF, in our hand, may be the septo-hippocampal pathway, the major cholinergic input to the HF[68-71]. The anatomical connections between the hippocampus and the septal area, through fibers in the fimbria-fornix system, have been well-known, for some time. Furthermore, the septo-hippocampal system has numerous functional cross-connections with other areas of the brain, such as the hypothalamus, locus coeruleus, periaqueductal gray matter, raphe magnus and cerebral cortex[72,73]. This

extensive connection makes it possible that peripheral noxious information, when arriving at the higher level of the brain, may indirectly get access to the HF by means of other pain-related areas. In this context, Dutar *et al*. [74] found that a large proportion of septo-hippocampal neurons (SHNs), which are at the origin of the cholinergic septo-hippocampal pathway, exhibited an activation pattern in response to peripheral somatic noxious stimulation. In the discussion, the authors explained the finding by saying "One could hypothesize that the responses of SHNs to noxious peripheral stimulation are due to the input coming from locus coeruleus, raphe nuclei, and/or other brainstem structures." In addition, several studies from Khanna's group have shown a modulatory effect of this sepo-hippocampal pathway on hippocampal neuronal responses to formalin-evoked pain[56-58,75]. A systemic description of the cholinergic modulation of pain processing in the HF, either behaviorally or electrophysiologically, will be presented below.

2.3 Efferents from the HF According to Henke[59], the efferents from the HF comprise two major systems: the dorsal pathway through the fimbria-fornix system and the ventral pathway via the entorhinal region. The fimbria-fornix connections are fairly well documented. Fornix fibers originate mostly in hippocampal field CA1 and project to the medial and lateral septum, the diagonal band nucleus, the anterior thalamus, the mammillary region, and the so-called limbic midbrain. Fimbria fibers originate in CA2, CA3, CA4 and the subicular complex and project to the anterior thalamus, the preoptic area, the hypothalamus, and the bed nucleus of the stria terminalis[76-78]. The ventral projection system connects the HF with the EC[38,79,80]. All these cortical and subcortical regions connected by the dorsal and ventral projection system are further associated with some pain-processing structures anatomically or functionally, thus providing a link between HF output and pain. Therefore, hippocampal activity would be expected to project to a number of limbic and cortical areas which may be involved in processing the motivational-affective component of pain[1].

3 Behavioral studies

3.1 Effects of activation of the HF on pain

3.1.1 Effects of the HF stimulation in animals There have been implications from previous stimulating studies that the HF might be involved in the aversive events processing. In the paper of Lico *et al*.[81], the authors observed that the guinea pig under light anesthesia showed a sequence of responses to a painful stimulation (dental pulp electrical stimulation), including defensive-offensive movements, autonomic manifestation (respiration) and high-pitched vocalization which are interpreted as signals of a subjective sensation of pain, and that stimulation of limbic structures such as the septum and dorsal hippocampus resulted in either analgesic-like or algesic-like effect, thus indicating limbic modulation in the perception of painful messages[81]. In contrast to the above-mentioned results in guinea pigs, Prado and Roberts[82] reported somehow contradictory results in rats. One hundred and fourteen sites in the rat brain have been stimulated with a gradient of increasing intensity and the aversive and antinociceptive thresholds determined for each site using the aversion analysis and tail-flick test. When it comes to the hippocampus, the results demonstrated that electrical stimulation of lateral and ventral hippocampus elicited neither aversion nor antinociception, while stimulation of dorsal and medial hippocampus caused strong antinociception without significant aversion[82]. The discrepancy may be due to differences in stimulation location and parameters, animal species, and pain assays. A similar finding from Yeung *et al*.[83] stimulated the hippocampus of three animals and found one site to be antinociceptive, but the aversiveness of the stimulation was not reported. Sinha *et al*.[84] found that stimulation of the hippocampus disrupts the jaw-opening reflex evoked by phasic tooth pulp pain in rats. Furthermore, there are still previous reports concerning stimulation of the anterior hippocampus in other species such as cats and monkeys, all of which could evoke pain-like behaviors[85].

The above-described stimulating experiments mainly focus on the limbic modulation of acute nociception. Then what about the roles of HF in modulating pathological pain processing? Abbott and his colleagues reported that electrical stimulation of the dorsal hippocampus resulted in a prolonged analgesia in the formalin test, a well-established ani-

mal model of tonic pain, when the stimulation produced epileptiform after-discharges[86]. However, repeated stimulation at levels that produced after-discharges abolished the analgesia.

3.1.2 Effects of the HF stimulation in humans Besides the stimulating studies carried out in the animals, earlier clinical observations on the human subjects also demonstrated that the hippocampus is involved in processing of noxious stimuli[87] and electrical stimulation of the HF evoked painful sensations in humans[88].

3.2 Effects of disruption of the HF on pain

3.2.1 Effects of hippocampal lesioning in animals

3.2.1.1 Hippocampectomy or surgical ablation Jackson and Regestein[89] examined the effects of partial or total hippocampal ablation on the performance of a prolonged titrated avoidance aversive schedule by the monkeys, a particularly useful model for assessing changes in pain sensation. They found that three of the four monkeys with total hippocampal damage were unable to continue for the entire session of the schedule compared with partial hippocampectomized monkeys and monkeys without hippocampal lesions. In addition, the authors also pointed out that the hippocampal cells which support prolonged titrating avoidance behavior are spread through the length of the hippocampus, rather than concentrated within a specified anterior or posterior location. Extensive hippocampectomy in other animal species, such as cats and baboons, has also been reported to result in a diminished reaction to pain[90,91].

3.2.1.2 Electrical lesion There have been a variety of previous reports studying the consequences of electrical lesion of hippocampus in animals. In one previous study, rats with electrical lesion in the medial part of the dorsal hippocampus were found to be more active than normal and brain damaged controls. This hyperactivity was manifested in a greater number of light-beam interruptions in an activity cage and in increased running speed in an unbaited T maze[92]. When placed in a situation involving inhibition of movement, rats with hippocampal lesion were unable to inhibit movement to avoid shock, suggesting impairment of passive avoidance behavior[92,93]. In another report, electrical lesions of the hippocampus resulted in increased open-field activity in rats[94], similar to the hyperactivity observed in the above paper[92] and other previous related experiments[95,96]. Moreover, significant decreases in shock-induced aggression was observed following electrical hippocampal lesions[94], consistent with previous findings from Blanchard and Blanchard[97].

3.2.1.3 Aspiration A significant advance in the experimental study of the relationship between brain lesions and avoidance conditioning was the distinction between active and passive avoidance tasks[98]. Subsequent experimentation has indicated that an equally important differentiation must be made between one-way and two-way active avoidance tasks[99]. There is a great deal of evidence to indicate that animals with lesions of the hippocampus are deficient in the performance of passive avoidance tasks[92,93,100]. Importantly, Olton and Isaacson[101] extended these findings by showing differential effects of hippocampal aspiration lesion on the acquisition and retention of two types of active avoidance tasks. Rats suffering from lesions of the hippocampus were found to be superior to control animals in the performance of a two-way active avoidance task, but were inferior to normal animals in the performance of a one-way active avoidance task. The performance increments found in the two-way task appeared only during acquisition training, while the decrements in the one-way task appeared during both acquisition and retention. Here, it is of necessity to note that lesions of dorsal and ventral hippocampus will produce different effects on active-avoidance tasks, as claimed by one previous study[102]. Differences between the dorsal and ventral areas of the hippocampus have been demonstrated anatomically in the rat[103] and physiologically in the cat[104], and there have been suggestions from work with both species that they might differ in function as well[105]. As regards the active avoidance tasks, this paper showed that dorsal electrolytic lesions in the hippocampus produced deficits in the acquisition of one-way avoidance, while ventral lesions produced somewhat facilitated avoidance. Therefore, it would seem necessary to consider the dorsal and ventral areas as functionally separate entities when evaluating roles of HF in various types of behaviors, including the pain perception (see below). To summarize discussions from avoidance paradigms, it seems that lesion of the hippocampus would lead to deficits or improve-

ments in all three types of avoidance tasks.

3.2.1.4 Neonatal chemical lesion Overviewing the literature will retrieve a few reports investigating effects of neonatal excitatory damage to the hippocampus by microinjection of chemicals on the neurodevelopment of pain perception. One study demonstrated clearly that neonatal lesion of the ventral hippocampus, via bilateral injection of ibotenic acid, altered the neurodevelopment of supraspinal (but not spinal) mechanisms involved in the control of acute thermal and mechanical nociception, revealed as decreased latency after puberty in the hot plate and paw pressure tests (both supraspinally mediated) but without effect in the tail-flick test that is mediated mostly at the spinal level[27]. This alteration cannot be attributed to ventral hippocampus lesion *per se* as similar lesions in adults did not produce the same effects. This negative result of ventral hippocampus lesion in adult rats, compared with positive influences of dorsal hippocampus stimulation/lesion mentioned above[81-83,86,92], further strengthened the idea that the dorsal and ventral hippocampus are functionally distinct[102]. One important implication from this paper is that although ventral hippocampus appears not to play essential roles in pain processing of adult rats, early lesion of the ventral part of the HF would predictably alter the development of nociception. In another study, concerning postnatal hippocampal lesion, it has been demonstrated that behavioral outcomes of such ventral hippocampal lesions in rats, are determined by early postnatal environmental variables, including social interactions[106]. Consistent with this assertion, another study of neonatal chemical hippocampal lesions reported different transfer of nociceptive sensitivity from rats with postnatal hippocampal lesions to control rats, i.e. their siblings with whom they were housed[36].

3.2.2 Effects of hippocampal lesioning in humans The above outlined papers were all concentrating on effects of bilateral hippocampal lesions on pain-related responses in animals, so what about the results from human subjects? As early as 1960s, Gol and Faibish have successively published two clinical reports showing effects of human hippocampectomy on pain relief in patients suffering from intractable pain[107,108]. There was usually appreciable reduction in pain following an extensive bilateral hippocampectomy, whereas the effectiveness of unilateral hippocampal ablation varied a lot and did not last for a long period. After hippocampectomy, the patients also showed flattening of affect and were relatively less concerned about the seriousness of their disease condition. With regard to the involvement of the HF in pain perception in humans, there is a classical description of the well-known patient H.M. with a surgical bilateral lesion of the hippocampus[109]. This patient was less sensitive to more intensive painful stimuli, whereas his capacity to detect light touch (pressure sensitivity) was preserved. Furthermore, H. M. could not be classically conditioned to electrical shocks, reportedly because the most intense level of electrical stimulation that could be administered safely was below his nociceptive threshold[110]. To sum up, these observations support the notion that hippocampal lesion can alter the perception of nociception and partially alleviate chronic pain.

3.3 Microinjection studies Several pieces of evidence have been accumulating to support the roles of HF in pain processing by virtue of microinjection of a diverse array of drugs (anesthetics, receptor antagonists, neuropeptides, enzyme inhibitors, neurotransmitter/neuromodulator antagonists, *etc*.) into the hippocampus. Here we will list these microinjection experimental studies and provide a full view of the relationship between HF manipulation and nociception modulation.

3.3.1 Lidocaine To interrupt the neuronal activity within the HF, regional analgesia of the DG region, a gate to the HF[39,41,48,49,54], was accomplished by bilateral microinfusion of 2% lidocaine into the DG area 20 min after subcutaneous injection of 2.5% buffered formalin but 10 min prior to behavioral investigation within the formalin test[32]. Noticeably, behavioral assessment commenced 30 min after formalin injection and ended 40 min later in this experiment. The early phase of formalin test was not evaluated. The results indicate that injection of lidocaine into the DG is capable of reducing a pre-existing formalin-induced tonic pain[32]. This analgesic effect is incremental in its onset and is considerably stronger when administered to the contralateral side of the injury. However, local anesthetic infusion into the DG 10 min prior to formalin injury failed to produce significant analgesia. A similar study from the same lab, examining effects of lidocaine

microinjection into the cingulum bundle, fornix and medial bulboreticular formation, also revealed a time-dependent analgesia in the formalin test, although the specific temporal patterns of lidocaine action varied[63]. Taken together, these results indicate that blocking neural transmission along both afferent[32] and efferent[63] hippocampal pathways could reduce pain-related behaviors in the formalin test.

3.3.2 NMDA receptor antagonists To date, there have been two reports studying the effects of blocking NMDA receptor activation in the HF on the nociceptive responses in the formalin test[33,34]. In the paper of McKenna and Melzack[33], the authors utilized almost the same experimental procedure as presented above except that the 1 μL 2% lidocaine solution was replaced by 3.75 μg/0.75 μL AP5. In addition, the exact time point of drug microinfusion also differs. In this study, the competitive NMDA receptor antagonist AP5 was bilaterally injected into the DG area, either 5 min before or 15 min after the onset of formalin injury. Also, both acute and tonic phases of formalin pain were evaluated. AP5 injected into the DG of the HF, prior to hindpaw irritation, reduced both acute and tonic behavioral responses of the formalin test; moreover, AP5 administered to the DG after the injury also effectively suppressed formalin-induced tonic pain. These results indicate that: (1) the DG of the HF serves as an important forebrain structure involved in the pain-related neural processing; and (2) NMDA-sensitive mechanisms in this part of the forebrain can influence both acute and tonic behavioral responses to formalin-induced injury. Nevertheless, bilateral injection of AP5 into the CA1 area of the HF failed to elicit any analgesia in the formalin test[33]. This finding is partially at odds with another previous study exploring antinociceptive effect of intra-hippocampal CA1 and DG injection of AP5 and MK-801, a non-competitive NMDA channel blocker[34]. In that study, AP5 (3.75 μg/0.75 μL) or MK-801 (3 μg/0.5 μL) administered into the DG region 5 min prior to formalin injection significantly reduced pain behaviors in both acute and tonic phases of the formalin test, which is in concurrence with the results from McKenna and Melzack[33]. In the CA1 region, injection of AP5 had no effect while injection of the effective dose of MK801 (3 μg/0.5 μL) produced a significant antinociceptive effect in the tonic, but not the acute phase. The authors further proposed that MK801 exerted its antinociceptive effect by inhibiting GABAergic interneurons in the hippocampal CA1 area[34]. It can be concluded, from all these two papers, that NMDA-sensitive mechanisms in the DG modulate both acute and tonic noxious sensory processing. On the contrary, the hippocampal CA1 region might modulate tonic pain behavior only, implicating possible differential involvement of hippocampal subregions in mediating pain processing[32-34].

3.3.3 Cholinergic agonists Acetylcholine (ACh) is one of the main neurotransmitters released in the hippocampus and plays an important role in hippocampal nociceptive processing. Here, we will only discuss behavioral experiments performed regarding cholinergic modulation of pain processing in the HF. There are still a large number of electrophysiological studies elucidating how Ach and atropine affects peripheral painful stimulus-modified excitability of the hippocampal neurons, as well as molecular/biochemical studies showing changes in Ach release or activity of Ach-synthesizing enzyme, choline acetyltransferase (ChAT), in the HF in response to a noxious stimulation. These two latter contents will be specified sequentially below.

On the basis of widely-accepted notion that central cholinergic mechanisms participate in the process of pain modulation[111-113] and the well-established cholinergic innervations into the hippocampus[70,114,115], Klamt and Prado[116], using the tail-flick test and calibrated pinch test, mapped the sites in the rat brain where intracerebral administration of carbachol, a drug exhibiting both muscarinic and nicotinic agonist properties, evoked antinociception. Among those structures containing sensitive sites are the temporal lobe of the ventral hippocampus and rostral aspect of the dorsal hippocampus, consonant with the above-mentioned stimulating experiments demonstrating strong antinociception by focal electrical stimulation of the HF[81-83,86] and with previously reported wide distribution of cholinergic receptors in this area[114].

Possible roles of cholinergic neurotransmission of the dorsal hippocampus in modulation of nociception were also investigated in another previous behavioral/pharmacological study, using the vocalization test in guinea pigs, where a peripheral noxious stimulus (electric shock applied to the

thigh) provoked the emission of a vocalization response by the animal, which was interpreted as a manifestation of pain. Additionally, the paper examined the participation of opioidergic and GABAergic systems in modulation of nociception and their interactions[29]. The results demonstrate that activation of the cholinergic or opioidergic system of the dorsal hippocampus promotes antinociception in guinea pigs, while GABAergic activation promotes pronociception. In addition, antinociception produced by cholinergic stimulation depends on opioid synapses present at the same site. On the other hand, antinociception observed after microinjection of morphine into the dorsal hippocampus occurs through the inhibition of tonically active GABAergic interneurons[29]. In summary, these two behavioral reports point towards to the conclusion that cholinergic systems are likely to play vital roles in modulating pain processing occurring in the HF.

3.3.4 5-Hydroxytryptamine (5-HT) receptor antagonists The anatomy of the serotonergic projection from the median raphe nucleus to the hippocampus in the rat has been well documented[116,117]. A sizeable body of evidence has also supported the involvement of 5-HT in pain modulation[118,119]. Subcortical serotonergic afferents to hippocampus might be excited during noxious stimulation[120]. According to these implications, Soleimannejad *et al*.[35] tested the role of 5-$HT_{2A/2C}$ receptors in the CA1 and DG in the formalin model of tonic pain. The 5-$HT_{2A/2C}$ receptor antagonist ritanserin was bilaterally injected into the CA1 area and DG of behaving rats 5 min before subcutaneous injection of formalin irritant. Nociceptive behaviors in both phases of the formalin test were significantly decreased by ritanserin, supporting the hypothesis that the HF may modify the processing of incoming nociceptive information through 5-$HT_{2A/2c}$ receptor-dependent mechanisms.

3.3.5 Noradrenaline Noradrenaline (NE) has been repeatedly implicated in the ability of mammalian organisms to respond effectively to challenging situations[121]. The locus coeruleus gives rise to most of the important central noradrenergic fibers supplying several brain structures including the septo-hippocampal system[72]. The relationship between the noradrenergic system and the septo-hippocampal activity has been demonstrated through several techniques[122,123]. Thus, an interaction between NE in the HF and pain modulation is reasonably expected. Although application of tail-pinch was found to elicit similar increase in hippocampal NE and serotonin release[120,124], evidence from animal experiments and clinical investigations has suggested that an antagonistic relationship exists between NE and 5-HT[125]. Intriguingly, the functional antagonism between NE and 5-HT also applies to the pain processing in the hippocampus. As reported in one previous study, NE and serotonin exerted dose-dependent but opposite modulating effects on behavioral reactivity to hot plate heat and footshock noxious stimulus when injected into the dorsal or ventral hippocampus of rats[126]. Specifically, NE injections resulted in an increase in the behavioral reactivity to painful stimuli, while 5-HT injections elicited a decrease in the sensitivity. Moreover, NE injections were more effective in increasing reactivity when injected into the dorsal hippocampus while 5-HT injections were more effective in decreasing behavioral reactivity when injected into the ventral hippocampus. When NE and 5-HT were injected simultaneously they resulted in no change in behavioral reactivity as compared to saline control injections[126]. These results confirm an important functional role for the interaction between NE and 5-HT in the pain processing in the HF.

3.3.6 Nitric oxide synthase inhibitor Nitric oxide (NO) is an important neuroregulatory agent present in the hippocampus, which has been implicated in many physiological and pathological brain processes including stress-induced analgesia[127] and nociceptive processing[128,129]. Given these considerations, Echeverry *et al*.[130] has investigated the effects of intrahippocampal administration of N^{ω}-nitro-*L*-arginine methyl ester hydrochloride (L-NAME), an inhibitor of NO synthase (NOS), on nociceptive behavioral responses in stressed and nonstressed rats. Unilateral microinjection of L-NAME (50-300 nmol/0.2 mL) into the DG of the dorsal HF significantly increased the tail-flick latency in animals submitted, 5 d before, to 2-h single restraint stress. Nonetheless, L-NAME failed to modify nociception in nonstressed rats[130]. This stress modulatory effect on antinociception caused by NOS inhibition in the HF was later

confirmed in the hot plate test[28]. Moreover, the same effect was detected after subchronic restraint stress episodes (i.e. 5 d after 5 repeated restraint episodes), indicating lack of tolerance for the stress-antinociception modulating effect[28]. The delayed antinociceptive effect of NOS inhibition in the HF, after a single or repeated restraint episode, is accompanied by significant increase in the number of NO-producing neurons in the HF and related brain structures such as the entorhinal cortex[28]. Summarizingly, the results suggest that the modulation of nociceptive processing by NO in the dorsal hippocampus is dependent on previous stress exposure and on poststress interval and that this stress-antinociception modulatory effect may involve plastic changes in the HF.

3.3.7 Platelet-activating factor receptor antagonists Platelet-activating factor (PAF) is a potent phospholipid mediator that participates in inflammatory responses (for review, see[131]), including formalin-induced nociception in rats[132]. Evidence suggests that PAF exerts cellular actions through two high affinity intracellular (i.e. microsomal) binding sites and a low-affinity plasma membrane receptor[133]. The anatomical locations at which PAF affects formalin-induced tonic inflammatory pain processing were recently elucidated by intra-hippocampal administration of PAF antagonists acting on either plasma membrane (BN 52021) or intracellular (BN 50730) PAF binding sites[134]. These two kinds of PAF receptor antagonists were administered into the contralateral CA1 region (with respect to the injected hindpaw) of rats 20 min prior to formalin insult. The data showed that intrahippocampal injection of BN 52021, but not BN 50730, decreased the late-phase of nociceptive response in the formalin test in a concentration-dependent manner, suggesting that hippocampal plasma membrane PAF receptors, but not intracellular PAF binding sites, mediate processing of painful information of an inflammatory nature in rats[134].

3.3.8 Vasoactive intestinal peptide The vasoactive intestinal peptide (VIP) is an essential neuropeptide widely distributed in the peripheral and central nervous systems[135], with a large spectrum of biological actions in mammals, including hormonal regulation, analgesia, neurotrophic and mediation of circadian rhythmicity[136]. In the hippocampus, VIP is expressed only in the interneurons[137]. VIP receptor subtypes have also been identified in the hippocampus[138]. Numerous studies provide compelling evidence for the implication of VIP in pain sensitivity[139]. On account of these statements, Ternianov *et al*.[140] demonstrated that unilateral or bilateral infusion of VIP into the hippocampal CA1 area dose-dependently increased the pain threshold compared to the control group. The intra-hippocampal VIP induced antinociception was repeated in a model of depression in rats[141]. In this paper, the authors firstly examined the pain threshold in bilateral olfactory bulbectomy (OBX) rats, a widely used animal model of depression. Then antinociceptive effects of VIP microinjected unilaterally or bilaterally into the hippocampal CA1 area were investigated by using an analgesy-meter test. It was found that: (1) the pain threshold was increased in the OBX rats when compared to the sham operated controls, implicating a correlation between depression and pain sensitivity; (2) VIP showed differential antinociceptive effects depending on the side and dose of administration. Microinjections of VIP into the left CA1 area and into both CA1 areas significantly increased the pain threshold in OBX rats, while there was no significant difference between right-side VIP-treated and right-side saline-treated OBX rats. These findings indicate that the hippocampal lateralized antinociceptive effect of VIP in OBX rats depends on the hemisphere of injection and that VIP-ergic neurons in the hippocampal CA1 area may play differential role in nociception of rats with a model of depression[141].

4 Electrophysiological studies

4.1 Electroencephalographic recording Besides the above-delineated behavioral evidence, there are substantial indications from electrophysiological studies that the HF is involved in pain mechanisms, among which is the electroencephalographic (EEG) recording in the hippocampus. As early as 1960s, Soulairac *et al*.[142] reported that strong electrical stimulation of the tail in conscious animals synchronized the hippocampal EEG and produced a 'hippocampal awakening' which lasted several seconds and was correlated with the rat vocalizing and biting the electrodes. Morphine and related agents blocked all of these responses[142]. Subsequently, Sinnamon and Schwartzbaum[143] examined the response of

dorsal hippocampal units and EEG responses, with respect to both slow-wave synchronous activity (4-12 Hz) and fast activity (20-40 Hz), to stimulation of rewarding sites in the lateral hypothalamus and of aversive sites in the dorsal tegmentum of the rat midbrain. It is concluded in this paper that rewarding and aversive brain stimulation can both produce, in the dorsal hippocampus of the rat, strong theta responses and non-specific increases or decreases in the activity of most units. Nevertheless, a selectivity of the hippocampal response is indicated by changes in fast EEG activity and in the activity of a relatively small number of units.

Another EEG study regarding hippocampus and nociception derives from Archer and Roth[144], who explored the pharmacodynamic relationship between thiopentone concentrations and both hippocampal EEG and nocifensive reflexes, measured as mechanical withdrawal threshold to noxious pressure stimulation on the tail. The results of this study showed that subanaesthetic concentrations of thiopentone enhanced hippocampal EEG power and reduced nocifensive reflex threshold in the same range of plasma concentrations[144]. The correlation between changes in nocifensive reflex threshold and total power in hippocampal EEG offered an indirect line of evidence in favor of hippocampus involvement in nociceptive processing.

4.2 Influences of cholinergic input on pain-evoked responses in the HF As outlined above, Ach, one of the most important neurotransmitters in the septo-hippocampal system, is supposed to play an important role in hippocampal processing of noxious information. A wealth of evidence has been presented by previous electrophysiological experiments showing that Ach and atropine could affect peripheral painful stimulus-modified excitability of the hippocampal neurons[74,145-147]. There is general agreement that cholinergic neurons in the medial septum and vertical limb of the diagonal band of Broca (MS-VLDBB) are the major source of cholinergic afferents to the HF[68,70]. Thus, Dutar *et al*.[74] identified septo-hippocampal neurons, by their antidromic response to the electrical stimulation of the fimbria, from the MS-VLDBB and characterized their firing properties (latency and frequency), nature of responsive stimuli (both mechanical and thermal stimulation), topography of receptive fields (tail, hindpaw, forepaw or the whole body surface), as well as types of response to peripheral stimulation (excitation, inhibition, rhythmic bursting activity). The predominant response of septo-hippocampal neurons to noxious stimulation is excitatory, suggesting that the activity of septo-hippocampal system is indeed increased during painful stimulation. Since the septo-hippocampal pathway is known to be a cholinergic pathway[69,71] and the dominant effect of ACh in the hippocampus is to facilitate pyramidal cells firing by various mechanisms[148,149], it follows that noxious stimulation should result in an increased activity of hippocampal neurons[74]. This assumption was further testified by Sinclair and Lo[146], who obtained almost the same results in the CA1 region of the dorsal HF. They found that none of the cells responded to non-noxious stimuli but 91 of 216 cells were excited by noxious stimuli (pinch and heating of the tail). The receptive fields of these nocifensive neurons were generally large, similar to pain-responding septo-hippocampal neurons[74]. However, this study failed to detect the significant effect of atropine, producing only transient changes of an inconsistent nature[146].

Besides the above two reports, there is another previous study determining electrophysiological patterns in the hilus of the DG in response to two different types of sensory stimuli: olfactory and noxious stimulation[145]. The results showed that noxious stimulation (tail clamp) produced a blockade of spontaneous slow waves (1-12 Hz) in the DG but did not increase fast wave activity in urethane-anaesthetized rats. This slow wave blockade was independent of olfaction but abolished by scopolamine hydrobromide, a central cholinergic antagonist.

The last paper regarding Ach and pain processing in the HF examined the effects of Ach, pilocarpine (a muscarinic acetylcholine receptor agonist) and atropine on pain-evoked responses of pain-excited neurons (PEN) and pain-inhibited neurons (PIN) in the hippocampal CA1 area of rats. The trains of electric impulses applied to the sciatic nerve were used as the noxious stimulation. The results showed that intrahippocampal microinjection of ACh (2 μg/1 μL) or pilocarpine (2 μg/1 μL) inhibited the electric activities of evoked discharges of PEN and potentiated those of PIN at the same

time, while atropine (0.5 μg/1 μL) produced opposite responses[147]. Overall, all of these four studies provide converging evidence that painful stimulation can indeed elicit electrophysiological changes in the septum and HF, the response pattern of which partially relies on the cholinergic inputs.

4.3 Involvement of HF in pain processing Since the early 1990s, Khanna's group has been continuously studying electrophysiological properties of hippocampal pyramidal and interneurons in response to acute and tonic painful stimulation and published a series of papers, providing convincing evidence for the involvement of HF in pain processing. The major publications about hippocampal electrophysiology and pain are listed below.

4.3.1 Depression of CA1 neuronal excitability by noxious heat stimulation As an initial step into dissecting electrophysiological responses of hippocampal CA1 neurons to pain, Khanna and Sinclair first discovered that a noxious heat stimulation applied to the tail produced a profound and prolonged depression of the dorsal hippocampal CA1 population spike which habituated upon subsequent exposures. Furthermore, this depression of neuronal transmission was found to be dependent on the hippocampal EEG state of the animal[150]. To further characterize this phenomenon, Khanna and Sinclair[75] reported that: (1) noxious stimulation-induced persistent depression and habituation were topographically represented; (2) noxious stimulus-induced CA1 synaptic depression was mediated at the apical dendritic region, involving postsynaptic changes in apical dendritic excitability and/or a presynaptic decrease in neurotransmitter release from CA3 afferent terminals; (3) the mechanism leading to synaptic depression involved Ach release in the apical dendrites of CA1 pyramidal cells upon activation of septo-hippocampal neurons by noxious stimuli.

4.3.2 Persistent pain-induced 'signal-to-noise' processing in the HF

4.3.2.1 Comparison of dorsal hippocampal field CA1 pyramidal cell responses between acute and persistent pain The two papers introduced above mainly focus on the effects of acute noxious stimulation, for example exposing the tail to a noxious hot water stimulus, then what about the effects of tonic, persistent painful stimulus? In 1997, Khanna published a classical paper describing essential differences in the dorsal hippocampal CA1 pyramidal cell responses to a persistent (formalin pain) versus an acute nociceptive stimulus[56]. The major differences lie in: (1) the duration of field rhythmic sinusoidal activity (RSA or theta rhythm); (2) the degree of CA1 pyramidal cell population spike amplitude depression; (3) the proportion of CA1 pyramidal cells excited relative to those suppressed by pain. A hindpaw injection of formalin, compared to acute noxious heat stimulus, produced a prolonged increase in the period of theta and a long-lasting depression of CA1 pyramidal cell synaptic excitability. More interestingly, formalin-evoked persistent pain selectively excited a discrete population of CA1 complex spike cells (putative pyramidal cells) with relatively higher spontaneous activity against the background of widespread pyramidal cell suppression, generating a 'signal-to-noise' response. Such response occurred in parallel with increased theta[56]. The author proposed that such formalin-induced 'signal-to-noise' processing might contribute to the affective-motivational component of pain.

4.3.2.2 Formalin-induced changes in hippocampal field CA1 interneuronal nociceptive responses An enormous variety of experiments suggest that during periods of extracellular theta, intracellularly recorded pyramidal cells will display a rhythmic, GABAergic inhibitory postsynaptic potential[151,152], whereas GABAergic interneurons in this region should depolarize and/or exhibit rhythmically modulated increased firing rates[152]. Thus, it is natural to speculate that formalin-induced suppression of CA1 pyramidal cell spike activity in correlation with local theta might involve a perisomatic inhibition via GABAergic inhibitory interneurons. To test this hypothesis, Zheng and Khanna[153] determined the changes in discharge rates and firing pattern (rhythmicity) of field CA1 putative inhibitory interneurons in response to a hindpaw formalin injection. The results showed that a majority of the extracellularly recorded dorsal CA1 putative GABAergic interneurons were excited rhythmically in conjunction with theta activation on formalin injection. This finding, in conjunction with the above descriptions, adds strength to the conclusion that the concerted excitation of rhythmically

modulated interneurons may underlie formalin-elicited extensive pyramidal cell suppression[153].

4.3.2.3 Morphine effect on formalin-induced pyramidal cell suppression and interneuronal activation In the study of Khanna and Zheng[154], concurrent systemic administration, or pre-treatment, of morphine sulphate reversed formalin-induced pyramidal cell suppression (population spike or extracellular activity) and theta activation in a dose-dependent and naloxone-reversible manner. Moreover, the authors declared that morphine sulphate exerted its actions via an effect on the septo-hippocampal neural processing, without any change in pyramidal cell basal extracellular responses or excitability[154]. In addition, concurrent administration of morphine and formalin also reduced the excitation of presumed interneurons in the dorsal field CA1 area with a decline in theta activity[153]. In summary, morphine could reverse formalin-induced pyramidal cell suppression and interneuronal activation, thus blocking the 'signal-to-noise' response in the dorsal hippocampal field CA1 area via its effect on septo-hippocampal neural network processing.

4.3.2.4 Modulation of formalin-induced nociceptive processing in the CA1 area by MS-VLDBB-derived cholinergic input As mentioned earlier in this review, the septo-hippocampal neurons, which are at the origin of the cholinergic septo-hippocampal pathway[71], are activated following peripheral noxious stimulation[69]. Secondly, the MS-VLDBB input to the HF, the major source of cholinergic afferents to this structure[68,70], is related to sensory events and exerts an inhibitory effect on CA1 neuronal activity[155]. Thirdly, the induction of theta activity is critically dependent upon MS-VLDBB cholinergic and GABAergic inputs to the hippocampus[156]. Fourthly, the cholinergic muscarinic receptor antagonist, atropine sulphate, when administered systemically in a dose that blocked theta activity or applied iontophoretically in the CA1 pyramidal cell dendritic region, prevented depression of CA1 population spike amplitude caused by noxious heat stimulation[75]. Fifthly, subcutaneous formalin injection produced complex changes in dorsal hippocampal activity of choline synthesizing enzyme choline acetyltransferase or Ach release (see below). Lastly, the septohippocampal cholinergic input, though might enhance the excitement of CA1 pyramidal cells (via disinhibition) at the cell body region[148,149], evokes a presynaptic inhibition of excitatory synaptic transmission across the apical dendrites of these neurons and increases the inhibitory GABAergic tonus impinging upon them[157]. Based on these considerations, Khanna[56] also tested whether the MS-VLDBB region is involved in those pain-evoked changes in CA1 pyramidal cell activities. Both the pyramidal cell suppression and theta activation were prevented by electrolytic lesions centered in the MS-VLDBB region, so did the signal-to-noise processing. More solid evidence favoring the involvement of MS-VLDBB in formalin-induced nociceptive processing in the HF has been suggested by another previous report from Khanna's lab, where the MS-VLDBB cholinergic neurons were selectively destroyed by intraseptal injection of an immunotoxin, 192 IgG-saporin[57]. In comparison to vehicle-treated animals, selective cholinergic destruction attenuated formalin-induced: (1) theta activation (amplitude but not frequency), (2) suppression of CA1 pyramidal cell population spike and dendritic field excitatory postsynaptic potential, (3) inhibition of complex spike cell extracellular activity and 'signal-to-noise' processing, and (4) excitation and theta-rhythmicity of local putative GABAergic interneurons. However, pretreatment with the immunotoxin did not alter the strength and proportion of complex spike cells excited following injection of formalin, indicating different neural networks for formalin-induced excitation[57]. Collectively, these results provide further support to the idea that formalin-induced theta activation, pyramidal cell suppression and 'signal-to-noise' processing are all influenced, at least partially, by a common network involving CA1 perisomatic inhibitory interneurons modulated by MS-VLDBB cholinergic inputs.

4.3.2.5 Involvement of intra-hippocampal tonic inhibition in the formalin-induced nociceptive processing in the CA1 area Given the results stated above, one can postulate that formalin-induced 'signal-to-noise' processing in CA1 is mediated, at least in part, by the excitation of the septohippocampal cholinergic neurons[56,57] which, in turn, activate a network of GABAergic inhibitory interneurons in CA1 to suppress the discharge of CA1 pyramidal cells[153,158]. To further verify the proposition, Zheng and Khanna[58] examined the effect of

disruption of intra-hippocampal GABAergic mechanisms (local application of bicuculline) on formalin-induced CA1 nociceptive responses, due to the well-documented roles of $GABA_A$ receptors in mediating tonic inhibition in the hippocampus[159]. It was found that ventral- (applied to the apical dendritic region), but not dorsal-bicuculline (applied to the pyramidal cell layer and stratum oriens) attenuated formalin-induced suppression of pyramidal cell extracellular discharge. The antagonism was selective in such a way that the excitation of pyramidal cell was unaffected. Altogether, the findings favor the notion that GABAergic mechanisms, especially in the region of apical dendrites, facilitate formalin-induced 'signal-to-noise' processing in part by masking a basal excitatory drive impinging upon pyramidal cells and consequently, biasing the majority towards greater susceptibility to inhibition (suppression of 'noise') on formalin injection[58].

4.3.3 Formalin-evoked changes in hippocampal theta state Theta wave activity refers to the sinusoidal pattern of hippocampal field activity at 3–12 Hz (3 to 6 Hz in anesthetized rat and 4–12 Hz in behaving animals), occurring spontaneously or in response to sensory stimuli, which reflects the intracellular membrane potential oscillations generated in CA1 pyramidal cells during processing of information[156,160]. Using extracellular electrophysiological recording techniques, Tai *et al*.[160] explored the temporal characteristics of hippocampal theta activation in relation to formalin nociception and demonstrated that hind paw injection of formalin evoked biphasic increase in duration of dorsal CA1 theta in behaving rats. The biphasic profile of theta activation broadly paralleled animal biphasic behavioral activation, especially lick and moment-to-moment agitated behaviors. Correspondingly, theta-modulated cell firing was also observed following formalin injection in the anesthetized rat[160]. However, it is worthy of noting that in the formalin model the theta state of the hippocampus reflects a neural drive that is dissociated or delinked from the duration of nociceptive experience and is not selective to the typical nociceptive indices of lick, flinch, and lift of the injured paw.

4.4 Pain-evoked synaptic plasticity in the HF Up to this point, the evidence has begun to accumulate that long-term plastic changes in sensory-related synapses are a key mechanism for chronic pain[161-164]. Unfortunately, there is still a paucity of basic research exploring pain-related synaptic plasticity in the HF[12,165]. Using *in vivo* electrophysiology, Wei *et al*.[165] first showed that hippocampal pyramidal cells responded to peripheral noxious stimuli in adult anesthetized rats. Then by slice electrophysiology, the authors found that in CA1 neurons, synaptic plasticity of excitatory glutamatergic transmission was altered after tissue injury, reflected as the enhancement of long-term potentiation (LTP), induced by a single tetanic stimulus in the CA1 region, after tail amputation in mice. Consistent with this finding is that subcutaneous injection of whole bee venom (BV) solution, a well-established animal model of persistent inflammatory pain experimentally mimicking honeybee sting-evoked natural tissue injury[166-171], also significantly enhanced the induction probability and the magnitude of LTP, elicited in both DG and CA1 area by theta burst stimulation (TBS), when compared to the control[12]. Notably, an important finding added by the latter study is that spatial features of neuronal plasticity, a less concerned phenomenon, were also dramatically altered after BV-induced persistent nociception, in that the synaptic connection size over the whole HF was robustly enlarged and the input-output function of individual synaptic efficacy was distinctly elevated[12]. Persistent pain-evoked spatial plasticity also resided in the deformation or split of the shape/structure of the fEPSP by a TBS conditioning under the state of persistent nociception[12]. These findings, coupled with those mentioned above, provide at least suggestive but compelling evidence that peripheral painful stimulation, when becomes persisting or severe, can result in long-term, intense and complicated changes in spatiotemporal neural plasticity in the HF.

5 Molecular and biochemical studies

5.1 Pain-induced changes in immediate early genes expression in the HF Immediate early genes (IEGs) are crucial intermediates in a cascade linking membrane stimulation to long-term alterations of neuronal activity[172,173]. Stressful and noxious stimuli induce not only short-lasting hormonal and behavioral modifications, but also lasting changes in numer-

ous physiological parameters, indicating profound alterations in protein synthesis. Accordingly, it is conceivable that peripheral noxious stimulation would probably lead to corresponding changes in IEG expression in the HF, to fulfill the necessary physiological and behavioral functions pertinent to pain. As a matter of fact, there have been certain amounts of previous studies disclosing the relationship between pain and hippocampal IEG expression and they will be addressed below.

5.1.1 c-Fos expression c-Fos is one of the most extensively studied and best characterized IEGs in the central nervous system. Actually, c-Fos expression has been widely used as a sensitive and reliable marker for neuronal activity throughout the neuroaxis following appropriate stimulation[174-176]. What's more, an enormous variety of experiments have been performed to elucidate pain-related c-Fos expression in the HF, but the data to date give an inconsistent picture.

5.1.1.1 Increase in c-Fos expression following painful stimulation in the HF There are mainly five papers, in our hands, reporting pain-evoked increase in c-Fos expression in the HF[165,177-180]. Aloisi *et al*.[177] investigated, by immunohistochemistry, the effects of a persistent painful stimulus (formalin injection) and restraint stress (immobilization) on c-Fos expression in the hippocampus and septum of male and female rats. The results displayed that in both male and female rats, unilateral injection of formalin induced bilateral c-Fos expression in the hippocampus, but the number of labeled neurons was two-fold higher in females than in males. Restraint stress was not effective in c-Fos induction in the hippocampus of both sexes. In the septum, both treatments increased c-Fos, but this increase tended to be greater in males than females[177]. It should be aware that formalin-treated and restrained animals were killed 90 min after the beginning of treatment. Based on this paper, Ceccarelli *et al*.[179] further tested the time course of formalin pain-provoked c-Fos expression in all hippocampal subregions. In male rats, at 2 h after formalin injection, a remarkable increase in c-Fos expression was detected in the DG and CA3, but this increase declined to the control level at 24 h. In formalin-treated females, c-Fos levels were lower, or tended to be lower, than control in all hippocampal subfields at 2 h and 24 h after formalin injection[179]. To conclude, formalin-induced persistent pain seem to have different effects on c-Fos expression in the hippocampus, depending on the time after treatment, the sex of the subject and the specific subregion analyzed. In 2001, Aloisi's group published another paper studying the interaction between gonadal hormone, nociceptive input and neuronal activity (c-Fos expression as the marker) in the hippocampus. In this study, formalin injection into the dorsal hindpaw was again found to produce an increase in c-Fos expression in the dorsal DG of both sexes of rats. The ventral subfields of male rats also displayed a higher c-Fos expression level[178].

The fourth paper reporting pain-increased c-Fos expression actually delineated the expression of various kinds of inducible transcription factors in response to noxious stimulation, including c-Fos, Fos B, c-Jun, Krox-24 and Krox-20[180]. In the case of c-Fos, the authors observed that a brief, strong electrical stimulation of sciatic nerve C-fibers induced little or no expression of c-Fos in the hippocampus. In contrast, this type of sciatic electrical stimulation, when coupled with a weak noxious cutaneous stimulation applied to one hindpaw simultaneously, a significant induction of c-Fos did occur[180]. Noxious stimulation (single or combined) also resulted in different temporal patterns of other IEGs expression, reflecting cell type-dependent complex sequences of events initiated by the C-fiber input. In this review, we will only focus on two IEGs: c-Fos and Krox-24 (see below).

The last related paper unraveled time-related changes in hippocampal c-Fos expression in response to tail amputation in mice. The major finding was that amputation of a mouse tail segment increased hippocampal c-Fos induction and this heightened c-Fox expression depended heavily on the peripheral sensory inputs and activation of NMDA receptors[165].

5.1.1.2 Decrease in c-Fos expression following painful stimulation in the HF There are also two previous studies reporting decreased c-Fos induction by painful stimulation. One is the work conducted by Funahashi *et al*.[181], who immunohistochemically examined changes in the c-*Fos* expression in both hippocampus and retrohippocampus, triggered by noxious mechanical stimulation of the mandibular incisor pulp. Whereas weak dentinal stimulation caused increases in c-

Fos expression in some regions which were not statistically significant, strong tooth pulp stimulation caused a bilateral decrease in c-*Fos* expression in almost every region, with the statistical significance reached in superficial layer of parasubiculum bilaterally, bilateral CA1 and ipsilateral side of superficial layer of medial entorhinal cortex[181]. The authors explained this result by stating that "inhibitory circuitry in hippocampal formation regions may be activated by peripheral noxious somatosensory inputs and this change in activity is accompanied by a change in the expression of the immediate early gene, c-fos." However, comparison of Aloisi's studies with this work would lead us to deduce that differences in a number of subtle experimental variables might contribute to the inconsistent results, such as the status of the animal subjecting to noxious stimulation (awake and anesthetized), stimulating site (hindpaw and mandibular incisor pulp), stimulus modality (chemical and mechanical), time point of perfusion (90 min, 2 h, 24 h and 2 h) and so on.

Even in the same formalin test, quite different results have been obtained from Khanna's group, who mapped the effect of different concentrations of formalin on the induction of c-Fos protein along the whole length of the hippocampus, including DG, CA3, the anterior-posterior and dorsal-ventral parts of the field CA1[30]. Although injection of saline increased induction of c-Fos along the length of hippocampus, injection of formalin decreased the number of c-Fos-positive cells in whole CA1, CA3 and DG, with a greater significant effect in the posterior–ventral regions of the hippocampus. In the discussion part of this paper, the authors mentioned one important reason for their contrasting results with Aloisi *et al*.[177]:

"The difference between present study and the previous study ... is partly because the latter compared change in Fos-positive cell counts following injection of formalin to that observed in non-injected animal. The basal induction of FLI in undisturbed, relatively non-stressed animals is generally low and, additionally, does not take into account the facilitatory effect of injection *per se* on induction of hippocampal FLI."[30]

5.1.2 Egr1 expression The zinc finger transcription factor Egr1, with the full name as early growth response protein 1 (also called NGFI-A, Krox-24, or zif/268), is critical for coupling extracellular signals to changes in cellular gene expression[182]. Wei *et al*.[165] found that either digit removal in rat or tail amputation in mice initiated a higher level of Egr1 expression in the hippocampus, whereas non-noxious heating or brush of the paw failed to induce marked Egr1 expression. Increased Egr1 activation was most dramatic in the CA1 region of the HF[165]. This pain-associated Egr1 induction, like the c-Fos (see above), is activity- and NMDA receptor-dependent. An important implication of these data is that Egr1 may act as an important regulator of pain-related neural processing in the HF.

As introduced above, Pearse *et al*.[180] also evaluated the temporal profile of Egr1 (called Krox-24 in that paper) expression initiated by noxious stimulation (sciatic electrical stimulation and/or noxious clamp of the hindpaw). Although a single brief electrical stimulation of the sciatic nerve failed to evoke an increase in the expression of Krox-24, combining these two stimuli, applied sequentially or simultaneously, strongly induced the Krox-24, indicating its possible role as "genetic coincidence detector" in the hippocampal pain processing[180].

5.2 Pain-induced changes in neurokinin-1 receptor and brain-derived neurotrophic factor expression in the HF The tachykinin neuropeptide substance P (SP) and brain-derived neurotrophic factor (BDNF), as well as their preferred receptors, neurokinin-1 (NK-1) receptor and tyrosine kinase B (TrkB) respectively, have been well accepted as mediators of nociceptive sensory information in somatosensory pathways in the central nervous system[183,184]. NK-1 receptors and BDNF have previously been implicated in nociception-induced spinal central sensitization[185-187]; however, the effects of painful stimuli on the expression of these two genes in the mood/affect and emotion-processing brain regions have not yet been characterized. In addition, their potential involvement in the neurobiology of stress-related mood disorders has also been demonstrated[188-190], suggesting that the effects of pain and stress may converge and activate similar neuronal pathways in the higher brain centers. Moreover, overwhelming evidence has been presented to support that stress can have profound effects on the hippocampus, a cen-

tral component of the limbic system involved in the regulation of mood or affect, including alteration in hippocampal structure[191], neural genesis[192], and synaptic plasticity[193,194] and so on. Implicit within these observations is the hypothesis that chronic pain may regulate the expression of NK-1 receptor and BDNF in the hippocampus in a manner similar to that exerted by stress. To address this issue, McCarson's lab has conducted lots of work by using multiple approaches, such as solution hybridization-nuclease protection assays[24,25,195], and in-situ hybridization[196]. One of the major insights that emerge from these studies is that both NK-1 receptor and BDNF mRNA levels are significantly attenuated by acute (formalin injection) or chronic pain (CFA injection), in accordance with the results initiated by acute or chronic restraint stress. These findings in the hippocampus are in sharp contrast to those uncovered in the spinal cord[25,186], potentially reflecting varied roles of these neuromodulators in the development of central sensitization in the sensory components of the central nervous system versus affective modulation of pain in the limbic structures. In addition, these results suggest that NK-1 and BDNF genes may provide useful molecular markers of hippocampal activation by pain, suggesting a possible role of these neuromediators in processing of pain in higher brain centers.

5.3 Pain-induced morphological changes in the HF One new gain of McCarson's work is that chronic inflammatory nociception (repeated injection of CFA into the hindpaw), but not acute pain (a single formalin injection), significantly reduced the neurogenesis in the DG area of the HF, measured by bromedeoxyuridine staining[196], similar to previous observations from various stress models[192,197]. This pain-induced decrease in hippocampal cell proliferation was recently confirmed by another immunoblotting study, comparing the apoptotic effects of chronic inflammatory pain and immobilization stress in rats[198]. In this report, repeated exposure to injections of 5% formalin gave rise to an increased ratio of Bax/Bcl-2 and activated caspase-3 in both lumbar spinal cord and hippocampus of both intact and adrenalectomized rats, implicating enhanced apoptosis in these two regions by chronic pain[198].

5.4 Pain-induced changes in the activation of extracellular signal-regulated kinase in the HF The generic term of mitogen-activated protein kinase (MAPK) is used to denote a family of signal transduction molecules that transduce a broad range of extracellular stimuli into diverse intracellular responses, by producing changes in transcriptional modulations of key genes as well as posttranslational modifications of target proteins[199]. The ERK (extracellular signal-regulated kinase) members of the MAPK family are originally identified as the primary effectors of growth factor receptor signaling[200] and supposed to regulate a wide array of cellular functions, including cell growth, differentiation, survival, as well as neuronal plasticity[201-203]. Nowadays, a growing number of reports also indicate that activated forms of ERKs would act both in the peripheral nociceptor terminal and the dorsal horn to produce pain hypersensitivity and hence contribute to the pathology of inflammatory and neuropathic pain[204-208]. Recently, our lab has performed series of behavioral, electrophysiological and biochemical experiments to examine potential roles of the MAPK signaling family in the development and maintenance of BV-induced pathological pain[209-216]. One of the papers relevant to this review is the immunoblotting study by Guo *et al*.[211], who determined the spatial and temporal expression and activation of two ERK isoforms, ERK1 and ERK2, in the spinal cord, primary somatosensory cortex (SI area of cortex), and hippocampus under normal, transient pain and persistent pain states. Intraplantar saline or BV injection, mimicking transient or persistent pain respectively, could equally initiate an intense and long-lasting activation of ERKs in all three areas examined, though ERK1 was more remarkably activated (phosphorylated) than ERK2 in the hippocampus[211]. Therefore, it appears that peripheral persistent nociception is also likely to induce a prolonged and profound change in the phosphorylation of the MAPK family of signaling molecules in the HF.

5.5 Pain-induced changes in Ach release in the HF Apart from the above described behavioral[29,217] and electrophysiological evidence[56,57,74,75,145-147] concerning the roles of cholinergic inputs in hippocampal processing of painful information, Aloisi's lab has addressed pain-elicited changes in Ach release or activity of Ach-synthesizing enzyme, ChAT,

in the HF in response to persistent pain stimulation. At first, Aloisi *et al*.[218] reported that unilateral formalin injection greatly impaired bilateral ChAT activity. Subsequently, Aloisi *et al*.[219] confirmed the result by showing that formalin injection reduced ChAT activity in male rats and increased adrenocorticotropic hormone in female rats. In addition, Alosi *et al*.[19] assessed the effects of novelty, persistent pain (formalin test) and stress (restraint) on hippocampal Ach release in male rats, by means of transversal microdialysis technique and high-performance liquid chromatography. While the introduction to a new environment (Novelty) induced in all rats higher ACh levels than baseline, formalin treatment decreased ACh release only in animals considered 'Inactive' during the Novelty phase. Restraint did not produce any modification of ACh release but increased corticosterone plasma levels both in sham- and formalin-treated animals. In conclusion, all these findings are compatible with the argument that formalin-induced persistent pain may indeed elicit a decrease in hippocampal ChAT activity or Ach release, at least in male rats. However, more strikingly, using almost the same experimental technique and design, Ceccarelli *et al*.[220] obtained opposite conclusions, that is, Ach release increased in both sexes of rats following formalin injection in terms of either raw values or the percentage of change.

6 Functional imaging studies

It has been generally believed that pain is characterized as a complex experience, dependent not only on the regulation of nociceptive sensory systems, but also on the activation of mechanisms that control mood-affect and emotion-cognition in higher brain centers[1,2,25,72,195,196,221]. The emergence of imaging approaches such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allows functional mapping of the intact brain and measurement of the responses in multiple areas simultaneously, thus bringing the study of pain into a deep level[13]. The involvement of the HF in pain processing has also been investigated using these functional imaging approaches. However, reports of pain-related responses in the hippocampal complex have been rare and contradictory in comparison with other areas. To date, no satisfactory explanations for these discrepancies have been provided, but possible causes are the variability in stimulus paradigms, experimental procedures, imaging tools (PET or fMRI), and other complementary variations. In the following paragraphs, we will present previous imaging studies performed on both animal and human subjects, reporting involvement of the HF in pain processing under various conditions.

6.1 Imaging studies in animals Compared to traditional human brain imaging, it is difficult to measure nociception-induced cerebral blood flow or metabolic changes in animals, although it is of particular importance to perform preclinical exploration of pain processing in the brain and evaluation of the efficacy of pain-relief drugs or strategies. Recently, Jaw's lab, using blood oxygenation level-dependent (BOLD) fMRI (combined with a refined atlas registration-based event-related analysis technique) and 18F-fluorodeoxyglucose small-animal PET respectively, successfully mapped formalin-induced nociceptive responses and activities in the whole rat brain[222,223]. Formalin-induced nociceptive processing resulted in increased BOLD signals or significant metabolic changes in a wide range of subcortical and cortical regions, demonstrating an activation pattern covering several parts of the nociceptive system, including bilateral cingulate cortex, motor cortex, primary/secondary somatosensory cortex, insular cortex, caudate putamen, periaqueductal gray, amygdala, thalamus, hypothalamus and bilateral hippocampus[222,223].

Overviewing the literature, there is still one previous study measuring pain-related global (gCBF) and regional cerebral blood flow (rCBF) changes in anesthetized cats[224]. In this paper, using PET with a camera specifically designed for use in small animals, the authors found that noxious inward or outward rotation of normal or inflamed elbow joints increased both gCBF and rCBF along the anterior to posterior axis of the cat brain. Of particular relevance is the finding that noxious rotations of the normal joint induced a significant increase in rCBF in the ipsilateral hippocampus, while the same stimulation of the inflamed joint produced an apparent increase in rCBF in both sides of the HF[224].

6.2 Imaging studies in human subjects

6.2.1 Imaging studies in normal human volunteers

6.2.1.1 Acute painful stimulation Several previous imaging

studies have been conducted on normal human subjects, using acute painful stimulation of the skin as the pain paradigm (for reviews, see[225,226]). If looked at carefully, one could find certain numbers of papers among them which have reported activation or de-activation of the HF by pain. Next, a brief list of these papers is presented.

6.2.1.1.1 Enhanced hippocampal activity by acute painful stimulation By adopting a promising paradigm of inflating an indwelling balloon catheter into a dorsal foot vein to induce vascular pain, Schneider *et al*.[227] elucidated the regional cerebral substrates subserving affective processing of acute pain. A correlation analysis was performed between the subjective ratings and fMRI data, revealing the main activated brain regions underlying affective aspects of pain, including amygdala, posterior cingulate cortex, superior temporal cortex, as well as the ipsilateral hippocampus[227]. Besides this study, there are still two additional papers reporting enhanced bilateral hippocampal activation by noxious heat stimulation measured by event-related fMRI[228,229].

6.2.1.1.2 Decreased hippocampal activity by acute painful stimulation In clear contrast with the above-described enhanced activation of HF by pain, there are also some results pointing to a decrease in hippocampal activity under the state of acute pain[230-232]. First of all, a model of acute traumatic nociceptive pain with concomitant autonomic/somatic reflexive response, by intracutaneous injection of a minute amount of ethanol into the lateral aspect of the right upper arm in normal human subjects, was found to elicit significant activation of the hypothalamus, periaqueductal gray, insular cortex, cingulate cortex, supplementary cortex and so on. Curiously, traumatic nociceptive pain resulted in a significant decrease in rCBF in the ipsilateral hippocampus[231]. Second, studies of brain processing of thermal pain with different intensities have obtained almost the same results regarding hippocampal responses to acute pain[230]. Using twelve healthy volunteers and PET, the rCBF responses to four intensities of stimulation, delivered by a CO2 laser, were recorded, ranging from warm (not painful), pain threshold (just painful), mildly painful or moderately painful. The following group subtractions were made to examine the changing cerebral responses as the stimulus intensity increased: (1) just painful - warm; (2) mild pain - warm; and (3) moderate pain - warm. In addition, rCBF changes were correlated with the subjective stimulus ratings. These comparisons and correlation analysis indicated a wide range of active regions associated with the multidimensional aspects of painful experience (for the details, see the original paper), and we will only discuss relevant findings related to the HF here. They are the follows: (1) comparisons of the warm stimulation with the 'just painful' state revealed significant rCBF decreases in the region of the contralateral para-hippocampal gyrus; (2) comparisons of warm with other painful states, such as 'mild pain', 'moderate pain', also disclosed reduced activation in the para-hippocampal gyrus region; (3) comparisons of 'mild pain' with warm revealed rCBF increases in the contralateral hippocampus but this increase no long existed when comparing 'moderate pain' with warm. The authors interpretated the hippocampal changes by stating that "the connections between ACC, insula and amygdala-hippocampal-prefrontal circuits constitute a network within which fear and contextual information relevant to pain can be integrated."

Finally, Peyron *et al*.[232] has revealed the effects of different attentional states on both pain perception and pain-related haemodynamic changes in the human brain using PET. For the details of the attentional modulation of pain and the underlying brain substrates, see the below description, but here, it is necessary to point out that, in this manuscript, noxious thermal stimulation, applied via a heat thermode, led to a decreased rCBF in the ipsilateral HF[232], in agreement with what has been discovered from the above mentioned two reports[230,231].

6.2.1.2 Abnormal pain processing in the HF In spite of the huge numbers of previous reports assessing the brain haemodynamic responses to experimental acute phasic or tonic thermal pain (for reviews, see[225,226]) there is no sufficient information, so far, about the brain processing of allodynia (perception of pain from a normally non-painful stimulus) in normal human subjects, although it is a very distressing painful syndrome frequently encountered in patients suffering from a variety of chronic pain conditions such as postherpetic neuralgia, peripheral neuropathies and reflex sympathetic dystrophy. Intradermal injection of

capsaicin, a main ingredient from hot chili peppers, elicits a strong acute pain accompanied by a multitude of sensory abnormalities including hyperalgesia (more pain to noxious stimuli) and allodynia[233,234]. Hence, Iadarola *et al*.[235] designed experiments to image regional brain activity in normal volunteers during capsaicin-induced intense pain and mechanical allodynia by using the PET $H_2{}^{15}O$-bolus method. They showed that the capsaicin stimulus immediately activated a widespread network of brain regions and a large, but only partially overlapping, set of regional activations occurred during the subsequent capsaicin-induced allodynia. When it came to the HF, two findings needed to be noted: (1) light brush, but not capsaicin-evoked acute pain, elicited activation of the contralateral hippocampus; (2) capsaicin-induced allodynia caused robust activation in the contralateral parahippocampal gyrus. These data raise the possibility that the HF and the para-hippocampus is also assumed to participate in the abnormal processing of allodynia[235].

6.2.1.3 Psychological modulation of pain perception

6.2.1.3.1 Attention Current research suggests that psychological state, such as attention, is able to modulate the perceived intensity and unpleasantness of painful experience. There has been ample evidence indicating attentional modulation of pain, in either behavioral[236] or electrophysiological[237] dimension. However, our understanding of the precise cognitive mechanisms and brain substrates behind this modulation of pain by attention remains poor. Peyron *et al*.[232] investigated with PET the influences on the haemodynamic brain responses exerted by selective manipulation of the attention allotted to a painful stimulus. The results identified, within the previously reported pain-activated areas, an intensity coding matrix superimposed on an attentional network. The attentional network could be further divided into a non-specific arousal component and a selective attention and orientating component. Nevertheless, in that study, the decrease of rCBF in the ipsilateral HF was only ascribed to affective-motivational response to pain and not further discussed by the authors[232]. In this regard, it is of great necessity to refer to another paper regarding imaging of the attentional modulation of pain[238], who examined using fMRI the predictions of attentional[239] and non-attentional[240] associative learning theories, demonstrating that hippocampal responses to pain varied as a function of attention. Attention was manipulated by varying the degree to which painful stimulation, or its omission, was surprising or unexpected. In that report, activation of the hippocampal system was detected during three types of mismatch: (1) novelty; (2) presentation of a stimulus when different or no stimulation is expected; (3) absence of an expected stimulus, as exemplified by unexpected omission of pain. Thus, one of the hippocampal functions in pain processing may resides in detecting mismatches between the expectation and the delivery of painful stimulation leading to increased attention[238]. Relevant to this finding is that from Bantick *et al*.[241], who elucidated the underlying neural systems and mechanisms involved in the phenomenon of reduced pain perception whilst attention is distracted away from noxious stimulus. When subjects were distracted during painful stimulation by an analogue of the Stroop task, many areas of the 'pain matrix' displayed reduced activation, including the HF[241]. The result showing that the hippocampal activity is reduced when attention is directed away from the painful stimulus is in concert with those findings of Ploghaus *et al*.[238] that the hippocampus is activated during attention to the noxious stimulation site.

6.2.1.3.2 Anxiety The positive relationship between anxiety and pain is a common experience in clinical settings[242]. Experimental studies have also confirmed the enhancing effect of anxiety on pain for different components and measures of pain, e.g., ratings of pain intensity[243] and unpleasantness[244], and pain threshold[245]. However, little is known about the human forebrain mechanisms underlying emotional modulation of pain, especially by anxiety. Using event-related fMRI, Ploghaus *et al*.[229] compared brain activation responses to noxious thermal stimulation while perceived pain intensity was manipulated by changes in either physical intensity or induced anxiety. They found that the entorhinal cortex of the HF responded differentially to identical noxious stimuli, dependent on whether the perceived pain intensity was enhanced by anxiety. Strikingly, pain modulation by temperature also activated the hippocampal formation, but the haemodynamic response originated in the more dorsal region of the hippocampus proper (see above). According to

the Gray-McNaughton theory, the authors explained the data by proposing that during anxiety, the HF amplifies the valence of aversive events to prime behavioral responses adaptive to the worst possible outcome of pain[229].

6.2.2 Imaging studies on patients Previous studies with normal volunteers have demonstrated widely-distributed cortical responses to experimental pain within a network of structures, including the thalamus, insula, anterior cingulate cortex, prefrontal, inferior parietal and somatosensory cortices. In addition, subcortical structures have also been involved in different processes that are closely linked to pain perception, such as basal ganglia, cerebellum, amygdala and hippocampus[228]. Subsequently, we will review some imaging studies performed on clinical patients suffering from various kinds of pain, where the HF has been detected to exhibit significant activation or de-activation in response to further painful stimulation.

One previous report was conducted on patients with acute nociceptive pain following surgical extraction of a lower impacted wisdom tooth[246]. In these patients suffering acute post-dental extraction pain, the cortical responses to further experimental heat pain, applied to the back of the right hand by heating thermodes, were examined using PET. As illustrated in the original paper, experimental heat pain in the surgical patients resulted in significant increases in rCBF in the ipsilateral prefrontal cortex, contralateral putamen and bilateral insula and clear decreases in rCBF in bilateral occipital cortex, ipsilateral posterior cingulate cortex, and ipsilateral hippocampus. This pain-induced decrease in hippocampal rCBF in patients suffering acute dental-extraction pain is in tandem with the results on normal human volunteers as mentioned above[230-232].

The pathophysiology of neuropathic pain due to peripheral nerve injury is not completely understood[247]. The peripheral nerve lesion may result in different clinical manifestations such as spontaneous ongoing pain and allodynia[247]. Petrovic *et al*.[248] explored the central processing of dynamic mechanical allodynia in patients with mononeuropathy with PET. In marked contrast with the work of Iadarola *et al*.[235] in normal volunteers, this study failed to observe an allodynia-related hippocampal activation but bilateral deactivations were revealed in the hippocampus/para-hippocampal gyrus, probably reflecting a meaningful suppression of brain systems subserving episodic memory and emotional response to aversive stimuli[248].

The last report imaging hippocampus and pain in patients measured rCBF changes during painful and silent myocardial ischemia induced by intravenous dobutamine infusion[249]. The results demonstrated that during both silent myocardial ischemia and angina pectoris, a significant activation of hippocampal gyrus was consistently detected, but the exact causes and functional significance of this hippocampal activation remained less understood[249].

7 Pain and memory

The involvement of HF in learning and memory has been validated by a tremendous variety of previous experiments and emerging evidence suggests that the HF is likely to participate in multiple forms of memory, including spatial navigation, declarative memory, recognition memory and so on[20-23,250,251]. Additionally, the abundant evidence presented in this review supports the hypothesis that the HF may also be involved in the manifold dimensions of pain processing, whilst on the other hand, pain of certain severity and persistence will produce significant influences upon the hippocampal morphology, metabolism and function. Then an interesting question arises: does the pain share common mechanisms with memory? To this point, there is still no definitive conclusion regarding this concern, but some investigators have devised insightful ideas that will be discussed here.

Synaptic plasticity is fundamental to many neurobiological functions, including memory and pain. The present mostly accepted synaptic and cellular model of pain hypersensitivity maybe the central sensitization occurring in the central nervous system[162,207,247]. Moreover, the mammalian hippocampal LTP is a widely studied model of activity-dependent changes in synaptic efficacy that is assumed to provide the physiological basis for learning and memory[252-254]. Consequently, Ji *et al*.[255] made a comparative analysis of the molecular mechanisms underlying the generation and maintenance of central sensitization and LTP, and found striking similarities between the two phenomena. However, there

is also an important mechanistic distinction between the two phenomena[255]. Consistent with this notion is the incrementing studies reporting induction of LTP in pain-related signaling pathways at each level of the neuromatrix. Actually, there have been a number of previous experiments investigating LTP phenomenon in multiple pain-related central nervous system regions, including the spinal cord dorsal horn[256,257], primary somatosensory cortex[258,259], amygdala[259,260], anterior cingulate cortex[163,164,261] and so on. With regard to HF, an enhanced LTP by pain was also reported by two previous studies[12,165]. To summarize, all of these reports have pointed unanimously to the strong resemblance and associations between pain and memory.

Despite these excitements, it is still far away from equating pain with LTP. As a matter of fact, there are indeed a wide array of problems that remain to be resolved. First, until now, not every area related to pain processing has been demonstrated to bear the ability to induce LTP; that is the question, whether the induction of LTP in pain pathways, as reviewed by Sandkühler[257], is a common phenomenon or just a characteristic feature of certain limited areas? Second, subtle differences do exist in the specific molecules underlying central sensitization and LTP[255]; Third, hippocampal LTP, accounting mainly for learning and memory, and LTP induced in pain pathways, indicative of pain signal amplification, may harness different sets of signaling transduction cascades for induction and maintenance; Last but not the least, our previous and ongoing work demonstrate that peripheral persistent nociception tends to produce indeed various forms of neural plasticity in the pain-related brain areas, with the specific pattern and extent of plasticity varying a lot depending on the individual regions analyzed. For example, as stated above, a long-term experience of persistent pain in the periphery could cause both spatial and temporal plasticity of synaptic connection, transmission and function in the HF[12], whilst our unpublished data suggest that persistent pain stimuli of similar intensity and duration would only induce spatial plasticity, but not temporal plasticity, in the ACC area, reflecting the complexity of brain dysfunction caused by the persistence of painful stimuli. Thus, pain-induced synaptic plasticity in the brain might be more complicated, manifested in the forms of not only temporal plasticity (LTP), but also spatial plasticity. In addition, there are also indications that chronic pain states can change the structure and morphology of the brain, namely central structural plasticity, which probably results in long-term dysfunction of synaptic transmission and modulation at different levels of the central nervous system[262,263]. Future experiments are certainly warranted to address these issues more clearly.

There have been numerous studies reporting disruption or functional impairment of memory formation or consolidation in chronic pain patients[8,10]. On the other hand, pain-related memory bias has also been frequently reported in patients with somatic pain disorders[264-266]. Nevertheless, whether pain-induced plastic changes in the HF contribute to these clinical symptoms remain less characterized. This is another critical issue entailing further elucidations.

8 Concluding remarks

The HF, an integral component of the limbic system and the hub of the 'Papez circuit', has long been recognized as playing an essential role in learning and memory. However, accumulating evidence from animal and human studies suggest that the HF may also bear significant associations with pain processing and also pain, when becomes persistent or chronic, could produce profound effects on hippocampal anatomy, metabolism, morphology and function. Novel information about modulation of sensitivity, plasticity, and activity of the hippocampus by painful stimuli may give us a better idea of how to control the negative emotional or cognitive consequences of pain, offering an alternative approach to the development of improved therapeutic regimens for treating comorbidities of chronic pain in the clinical setting.

Acknowledgements: This work was supported by the National Basic Research (973) Program of China (No. 2006CB500800), National Innovation Team Program of Ministry of Education, China (No. IRT0560), National Natural Science Foundation of China (No. 30670692 and 30770668).

References:

[1] Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain. In: Kenshalo DR Ed. The skin senses. Springfield (IL): Charles C. Thomas, 1968, 423-439.

[2] Price DD. Psychological mechanisms of pain and analgesia. Seattle: IASP Press, 1999.

[3] Bushnell MC, Apkarian AV. Representation of pain in the brain. In: McMahon SB, Koltzenburg M Ed. Wall and Melzack's Textbook of Pain, 5th edition. China: Elsevier Ltd., Churchill Livingstone, 2006, 107-124.

[4] Rainville P. Brain mechanisms of pain affect and pain modulation. Curr Opin Neurobiol 2002, 12: 195-204.

[5] Willis WD. Nociceptive pathways: anatomy and physiology of nociceptive ascending pathways. Philos Trans R Soc Lond B Bio Sci 1985, 308: 253-268.

[6] Melzack R. Evaluation of the neuromatrix theory of pain. Pain Pract 2005, 5: 85-94.

[7] Melzack R. The future of pain. Nat Rev Drug Discov 2008, 7: 629.

[8] Dick BD, Rashiq S. Disruption of attention and working memory traces in individuals with chronic pain. Anesth Analg 2007, 104: 1223-1229.

[9] Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence chronic pain? A review. Clin J Pain 1997, 13: 116-137.

[10] Ling J, Campbell C, Heffernan TM, Greenough CG. Short-term prospective memory deficits in chronic back pain patients. Psychosom Med 2007, 69: 144-148.

[11] Narita M, Kaneko C, Miyoshi K, Nagumo Y, Kuzumaki N, Nakajima M *et al*. Chronic pain induces anxiety with concomitant changes in opioidergic function in the amygdala. Neuropsychopharmacology 2006, 31: 739-750.

[12] Zhao XY, Liu MG, Yuan DL, Wang Y, Zhang FK, Chen XF *et al*. Nociception-induced spatial and temporal plasticity of synaptic connection and function in the hippocampal formation of rats: a multi-electrode array recording. Mol Pain 2009 (in press).

[13] Casey KL. The imaging of pain: background and rationale. In: Casey KL, Bushnell MC Ed. Pain imaging. Seattle: IASP Press, 2000, 1-29.

[14] Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. Science 1991, 251: 1355-1358.

[15] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007, 55: 377-391.

[16] Treede RD, Kenshal DR, Gracely RH, Jones AKP. The cortical representation of pain. Pain 1999, 79: 105-111.

[17] Duvernoy HM. The Human Hippocampus. Berlin: Springer-Verlag, 2005.

[18] Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiat 1937, 38: 725-744.

[19] Aloisi AM, Casamenti F, Scali C, Pepeu G, Carli G. Effects of novelty, pain and stress on hippocampal extracellular acetylcholine levels in male rats. Brain Res 1997, 748: 219-226.

[20] Bird CM, Burgess N. The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 2008, 9: 182-194.

[21] Eichenbaum H. Conscious awareness, memory and the hippocampus. Nat Neurosci 1999, 2: 775-776.

[22] Eichenbaum H. A cortical–hippocampal system for declarative memory. Nat Rev Neurosci 2000, 1: 41-50.

[23] Jaffard R, Meunier M. Role of the hippocampal formation in learning and memory. Hippocampus 1993, 3: 203-217.

[24] Duric V, McCarson KE. Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress. Neuroscience 2005, 133: 999-1006.

[25] Duric V, McCarson KE. Neurokinin-1 (NK-1) receptor and brain-derived neurotrophic factor (BDNF) gene expression is differentially modulated in the rat spinal dorsal horn and hippocampus during inflammatory pain. Mol Pain 2007, 3: 32.

[26] Oddie SD, Bland BH. Hippocampal formation theta activity and movement selection, Neurosci Biobehav Rev 1998, 22: 221-231.

[27] Al Amin HA, Atweh SF, Jabbur SJ, Saade NE. Effects of ventral hippocampal lesion on thermal and mechanical nociception in neonates and adult rats. Eur J Neurosci 2004, 20: 3027-3034.

[28] Echeverry MB, Guimarães FS, Del Bel EA. Acute and delayed restraint stress-induced changes in nitric oxide producing neurons in limbic regions. Neuroscience 2004, 125: 981-993.

[29] Favaroni Mendes LA, Menescal-de-Oliveira L. Role of cholinergic, opioidergic and GABAergic neurotransmission of the dorsal hippocampus in the modulation of nociception in guinea pigs. Life Sci 2008, 83: 644-650.

[30] Khanna S, Chang LS, Jiang F, Koh HC. Nociception-driven decreased induction of Fos protein in ventral hippocampus field CA1 of the rat. Brain Res 2004, 1004: 167-176.

[31] Lathe R. Hormones and the hippocampus. J Endocrinol 2001, 169: 205-231.

[32] McKenna JE, Melzack R. Analgesia produced by lidocaine microinjection into the dentate gyrus. Pain 1992, 49: 105-112.

[33] McKenna JE, Melzack R. Blocking NMDA receptors in the hippocampal dentate gyrus with AP5 produces analgesia in the formalin pain test. Exp Neurol 2001, 172: 92-99.

[34] Soleimannejad E, Naghdi N, Semnanian S, Fathollahi Y, Kazemnejad A. Antinociceptive effect of intra-hippocampal CA1 and dentate gyrus injection of MK801 and AP5 in the formalin

test in adult male rats. Eur J Pharmacol 2007, 562: 39-46.

[35] Soleimannejad E, Semnanian S, Fathollahi Y, Naghdi N. Microinjection of ritanserin into the dorsal hippocampal CA1 and dentate gyrus decrease nociceptive behavior in adult male rat. Behav Brain Res 2006, 168: 221-225.

[36] Yamamotová A, Franìk M, Vaculín Š, Šťastny´F, Bubeníková-Valešová V, Rokyta R. Different transfer of nociceptive sensitivity from rats with postnatal hippocampal lesions to control rats. Eur J Neurosci 2007, 26: 446-450.

[37] Teyler TJ, DiScenna P. The topological anatomy of the hippocampus. Brain Res Bull 1984, 12: 711-719.

[38] van Strien NM, Cappaert NLM, Witter MP. The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network. Nat Rev Neurosci 2009, 10: 272-282.

[39] Amaral DG, Witter MP. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 1989, 31: 571-591.

[40] Amaral DG, Lavenex P. The Hippocampus Book. New York: Oxford Univ Press, 2007.

[41] Jones RSG. Entorhinal-hippocampal connections: a speculative view of their function. Trends Neurosci 1993, 16: 58-64.

[42] Wyss JM. An autoradiographic study of the efferent connections of the entorhinal cortex in the rat. J Comp Neurol 1981, 199: 495-512.

[43] Cajal SR. The structure of Ammon's Horn (trans. L Kraft). Springfield, MA: CC Thomas, 1968.

[44] Dolorfo CL, Amaral DG. Entorhinal cortex of the rat: topographic organization of the cells of origin of the perforant path projection to the dentate gyrus. J Comp Neurol 1998, 398: 25-48.

[45] Witter MP, Groenewegen HJ, Lopes da Silva FH, Lohman AH. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog Neurobiol 1989, 33: 161-253.

[46] Kohler C. A projection from the deep layers of the entorhinal area to the hippocampal formation in the rat brain. Neurosci Lett 1985, 56: 13-19.

[47] Witter MP, Griffioen AW, Jorritsma-Byham B, Krijnen JL. Entorhinal projections to the hippocampal CA1 region in the rat: an underestimated pathway. Neurosci Lett 1988, 85: 193-198.

[48] Hjorth-Simonsen A, Jeune B. Origin and termination of the hippocampal perforant path in the rat studied by silver impregnation. J Comp Neurol 1972, 144: 215-232.

[49] Steward O. Topographic organization of the projections from the entorhinal area to the hippocampal formation of the rat. J Comp Neurol 1976, 167: 285-314.

[50] Steward O, Scoville SA. Cells of origin of entorhinal cortical afferents to the hippocampus and fascia dentata of the rat. J Comp Neurol 1976, 169: 347-370.

[51] Colbert CM, Levy WB. Electrophysiological and pharmacological characterization of perforant path synapses in CA1 mediation by glutamate receptors. J Neurophysiol 1992, 68: 1-8.

[52] Doller HJ, Weight FF. Perforant pathway activation of hippocampal CA1 stratum pyramidale neurons: electrophysiological evidence for a direct pathway. Brain Res 1982, 237: 1-13.

[53] Empson RM, Heinemann U. The perforant path projection to hippocampal area CA1 in the rat hippocampal-entorhinal cortex combined slice. J Physiol 1995, 484: 707-720.

[54] Lømo T. Patterns of activation in a monosynaptic cortical pathway: the perforant path input to the dentate area of the hippocampal formation. Exp Brain Res 1971, 12: 18-45.

[55] Yeckel MF, Berger TW. Feedforward excitation of the hippocampus by afferents from the entorhinal cortex: redefinition of the role of the trisynaptic pathway. Proc Natl Acad Sci 1990, 87: 5832-5836.

[56] Khanna S. Dorsal hippocampus field CA1 pyramidal cell responses to a persistent versus an acute nociceptive stimulus and their septal modulation. Neuroscience 1997, 77: 713-721.

[57] Zheng F, Khanna S. Selective destruction of medial septal cholinergic neurons attenuates pyramidal cell suppression, but not excitation in dorsal hippocampus field CA1 induced by subcutaneous injection of formalin. Neuroscience 2001, 103: 985-998.

[58] Zheng F, Khanna S. Intra-hippocampal tonic inhibition influences formalin pain-induced pyramidal cell suppression, but not excitation in dorsal field CA1 of rat. Brain Res Bull 2008, 77: 374-381.

[59] Henke PG. The telencephalic limbic system and experimental gastric pathology: a review. Neurosci Biobehav Rev 1982, 6: 381-390.

[60] Domesick VB. The fasciculus cinguli in the rat. Brain Res 1970, 20: 19-32.

[61] Pandya J. The connections of the cingulate gyrus. Exp Brain Res 1981, 42: 319-330.

[62] Foltz EL, White LE. Pain "relief" by frontal cingulumotomy. J Neurosurg 1962, 19: 89-100.

[63] Vaccarino AL, Melzack R. Temporal processes of formalin pain: differential role of the cingulum bundle, fornix pathway and medial bulboreticular formation. Pain 1992, 49: 257-271.

[64] Friedman DP, Murray EA, O'Neill JB, Mishkin M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. J Comp Neurol 1986, 252: 323-347.

[65] Mesulam MM, Mufson EJ. Insula of the old world monkey. III: Efferent cortical output and comments on function. J Comp Neurol. 1982, 212: 38-52.

[66] Klossika I, Flor H, Kamping S, Bleichhardt G, Trautmann N, Treede RD *et al*. Emotional modulation of pain: a clinical perspective. Pain 2006, 124: 264-268.

[67] Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000, 288: 1769-1772.

[68] Amaral DG, Kurz J. An analysis of the origins of the cholinergic and noncholinergic septal projections to the hippocampal formation of the rat. J Comp Neurol 1985, 240: 37-59.

[69] Dutar P, Bassant MH, Senut MC, Lamour Y. The septohippocampal pathway: structure and function of a central system. Physiol Rev 1995, 75: 393-427.

[70] Fibiger HC. The organization and projections of cholinergic neurons of the mammalian forebrain. Brain Res Rev 1982, 257: 327-388.

[71] Fonnum F, Walaas I. The effect of intrahippocampal kainic acid injections and surgical lesions on neurotransmitters in the hippocampus and septum. J Neurochem 1978, 31: 1173-1181.

[72] Aloisi AM. Sex differences in pain-induced effects on the septohippocampal system. Brain Res Rev 1997, 25: 397-406.

[73] Swanson LW, Cowan WM. The connections of the septal region in the rat. J Comp Neurol 1979, 186: 621-656.

[74] Dutar P, Lamour Y, Jobert A. Activation of identified septohippocampal neurons by noxious peripheral stimulation. Brain Res 1985, 328: 15-21.

[75] Khanna S, Sinclair JG. Responses in the CA1 region of the rat hippocampus to a noxious stimulus. Exp Neurol 1992, 117: 28-35.

[76] Meibach RC, Siegel A. Efferent connections of the hippocampal formation in the rat. Brain Res 1977, 124: 197-224.

[77] Powell EW, Hines G. Septohippocampal interface. In: Isaacson RL, Pribram KH Ed. The Hippocampus. New York: Plenum, 1975.

[78] Siegel A, Ohgami S, Edinger H. Projections of the hippocampus to the septal area in the squirrel monkey. Brain Res 1975, 99: 247-260.

[79] Hjorth-Simonsen A. Hippocampal efferents to the ipsilateral entorhinal area: an experimental study in the rat. J Comp Neurol 1971, 142: 417-437.

[80] Swanson LW, Cowan WM. An audioradographic study of the organization of efferent connections of the hippocampal formation in the rat. J Comp Neurol 1977, 172: 48-84.

[81] Lico MC, Hoffmann A, Covian MR. Influence of some limbic structures upon somatic and autonomic manifestations of pain. Physiol Behav 1974, 12: 805-811.

[82] Prado WA, Roberts HT. An assessment of the antinociceptive and aversive effects of stimulating identified sites in the rat brain. Brain Res 1985, 340: 219-238.

[83] Yeung JC, Yaksh TL, Rudy TA. Concurrent mapping of brain sites for sensitivity to the direct application of morphine and focal electrical stimulation in the production of antinociception in the rat. Pain 1977, 4: 23-40.

[84] Sinha R, Sharma R, Mathur R, Nayar U. Hypothalamo-limbic involvement in modulation of tooth-pump stimulation evoked nociceptive response in rats. Indian J Physiol Pharmacol 1999, 43: 323-331.

[85] MacLean PD, Delgado JMR. Electrical and chemical stimulation of frontotemporal portion of limbic system in the waking animal. Electroenceph Clin Neurophysiol 1953, 5: 91-100.

[86] Abbott FV, Melzack R. Analgesia produced by stimulation of limbic structures and its relation to epileptiform after-discharges. Exp Neurol 1978, 62: 720-734.

[87] Delgado JM. Cerebral structures involved in transmission and elaboration of noxious stimulation. J Neurophysiol 1955, 18: 261-275.

[88] Halgren E, Walter RD, Cherlow DG, Crandall PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain 1978, 101: 83-117.

[89] Jackson WJ Regestein QR. Hippocampal lesions impair prolonged titrated avoidance by rhesus monkey. Exp Neurol 1979, 63: 28-34.

[90] Gol A, Kellaway P, Shapiro M, Hurst CM. Studies of hippocampectomy in the monkey, baboon and cat. Behavioral changes and a preliminary evaluation of cognitive functions. Neurology 1963, 13: 1031-1041.

[91] Schreiner L, Kling A. Behavioral changes following rhinocephalic injury in the cat. J Neurophysiol 1953, 16: 643-659.

[92] Teitelbaum H, Milner P. Activity changes following partial hippocampal lesions in rats. J Comp Physiol Psychol 1963, 56: 284-289.

[93] Blanchard RJ, Fial R. Effects of limbic lesions on passive avoidance and reactivity to shock. J Comp Physiol Psychol 1968, 66: 606-612.

[94] Eichelman BS. Effect of subcortical lesions on shock-induced aggression in the rat. J Comp Physiol Psychol 1971, 74: 331-339.

[95] Kimble DP. The effects of bilateral hippocampal lesions in rats. J Comp Physiol Psychol 1963, 56: 273-283.

[96] Roberts WW, Dember WN, Brodwick M. Alteration and exploration in rats with hippocampal lesions. J Comp Physiol Psychol 1962, 55: 695-700.

[97] Blanchard RJ, Blanchard DC. Limbic lesions and reflexive fighting. J Comp Physiol Psychol 1968, 66: 603-605.

[98] McCleary RA. Response specificity in the behavioral effects of limbic system lesions in the cat. J Comp Physiol Psychol 1961, 54: 605-613.

[99] Olton DS, Isaacson RL. Importance of spatial location in active

avoidance tasks. J Comp Physiol Psychol 1968, 65: 535-539.

[100]Douglas RJ. The hippocampus and behavior. Psychol Bull 1967, 67: 416-442.

[101]Olton DS, Isaacson RL. Hippocampal lesions and active avoidance. Physiol Behav 1968, 3: 719-724.

[102]Nadel L. Dorsal and ventral hippocampal lesions and behavior. Physiol Behav 1968, 3: 891-900.

[103]Segal M, Landis S. Afferents to the hippocampus of the rat studied with the method of retrograde transport of horseradish peroxidase. Brain Res 1974, 87: 1-15.

[104]Elul R. Regional differences in the hippocampus of the cat. I. Specific discharge patterns of the dorsal and ventral hippocampus and their role in generalized seizures. Electroenceph Clin Neurophysiol 1964, 16: 470-488.

[105]Andy OJ, Peeler DF Jr, Foshee DP. Avoidance and discrimination learning following hippocampal ablation in the cat. J Comp Physiol Psychol 1967, 64: 516-519.

[106]Wood G, Marcotte ER, Quirion R, Srivastava L. Strain differences in the behavioural outcome of neonatal ventral hippocampal lesions are determined by postnatal environment and not genetic factors. Eur J Neurosci 2001, 14: 1030-1034.

[107]Gol A, Faibish GM. Hippocampectomy for relief of intractable pain. Tex Med 1966, 62: 76-79.

[108]Gol A, Faibish GM. Effects of human hippocampal ablation. J Neurosurg 1967, 26: 390-398.

[109]Hebben N, Corkin S, Eichenbaum H, Shedlack K. Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M. Behav Neurosci 1985, 99: 1031-1039.

[110]Corkin S. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M.. Sem Neurol 1984, 4: 249-259.

[111]Aloisi AM, Ceccarelli I, Cavallaro K, Scaramuzzino A. 192 IgG-saporin induced selective cholinergic denervation modifies formalin pain in male rats. Analgesia 2002, 6: 19-25.

[112]Bartolini A, Ghelardini C, Fantetti L, Malcangio M, Malmberg-Aiello P, Giotti A. Role of muscarinic receptor subtypes in central antinociception. Br J Pharmacol 1992, 105: 77-82.

[113]Green PG, Kitchen I. Antinociception opioids and the cholinergic system. Prog Neurobiol 1986, 26: 119-146.

[114]Levey AI, Edmunds SM, Koliatsos V, Wiley RG, Heilman CJ. Expression of m1-m4 muscarinic acetylcholine receptor proteins in rat hippocampus and regulation by cholinergic innervation. J Neurosci 1995, 15: 4077-4092.

[115]Woolf NJ, Eckenstein F, Butcher LL. Cholinergic systems in the rat brain: I. Projections to the limbic telencephalon. Brain Res Bull 1984, 13: 751-784.

[116]Acsady L, Halasy K, Freund TF. Calretinin is present in nonpyramidal cells of the rat hippocampus. III. Their inputs from the median raphe and medial septal nuclei. Neuroscience 1993, 52: 829-841.

[117]Moore RY, Halaris AE. Hippocampal innervation by serotonin neurons of the midbrain raphe in the rat. J Comp Neurol 1975, 164: 171-184.

[118]Obata H, Saito S, Ishizaki K, Goto F. Antinociception in rat by sarpogrelate, a selective 5-HT2A receptor antagonist, is peripheral. Eur J Pharmacol 2000, 404: 95-102.

[119]Wei H, Pertovaara A. 5-HT1A receptors in endogenous regulation of neuropathic hypersensitivity in the rat. Eur J Pharmacol 2006, 535: 157-165.

[120]Kalén P, Rosegren E, Lindvall O, Björklund A. Hippocampal noradrenaline and serotonin release over 24 Hours as measured by the dialysis technique in freely moving rats: correlation to behavioural activity state, effect of handling and tail-pinch. Eur J Neurosci 1989, 1: 181-188.

[121]Glavin GB. Stress and brain noradrenaline: a review. Neurosci Biobehav Rev 1985, 9: 233-243.

[122]Abercrombie ED, Keller RW, Zigmond MJ. Characterization of hippocampal norepinephrine release as measured by microdialysis perfusion: pharmacological and behavioral studies. Neuroscience 1988, 3: 897-904.

[123]Compton DM, Dietrich KL, Smith JS, Davis BK. Spatial and non-spatial learning in the rat following lesions to the nucleus locus coeruleus. NeuroReport 1995, 7: 177-182.

[124]Rosario LA, Abercrombie ED. Individual differences in behavioral reactivity correlation with stress-induced norepinephrine efflux in the hippocampus of Sprague-Dawley rats. Brain Res Bull 1999, 48: 595-602.

[125]Samanin R, Garattini S. The serotonergic system in the brain and its possible functional connections with aminergic systems. Life Sci 1975, 17: 1201-1210.

[126]Gage FH, Springer JE. Behavioral assessment of norepinephrine and serotonin function and interaction in the hippocampal formation. Pharmacol Biochem Behav 1981, 14: 815-821.

[127]Spinella M, Bodnar RJ. Nitric oxide synthase inhibition selectively potentiates swim stress antinociception in rats. Pharmacol Biochem Behav 1994, 47: 727-733.

[128]Haley JE, Dickenson AH, Schachter M. Electrophysiological evidence for a role of nitric oxide in prolonged chemical nociception in the rat. Neuropharmacology 1992, 31: 251-258.

[129]Meller ST, Cumming CP, Traub RJ, Gebhart GF. The role of nitric oxide in the development and maintenance of the hyperalgesia produced by intraplantar injection of carrageenan in the rat. Neuroscience 1994, 60: 367-374.

[130]Echeverry MB, Guimarães FS, Oliveira MA, do Prado WA, Del Bel EA. Delayed stress-induced antinociceptive effect of nitric

oxide synthase inhibition in the dentate gyrus of rats. Pharmacol Biochem Behav 2002, 74: 149-156.

[131]Vane JR, Bakhl YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol 1998, 38: 97-120.

[132]Teather LA, Magnusson JE, Wurtman RJ. Platelet-activating factor antagonists decrease the inflammatory nociceptive response in rats. Psychopharmacology 2002, 163: 430-433.

[133]Marcheselli VL, Rossowska MJ, Domingo MT, Braquet P, Bazan NG. Distinct platelet-activating factor binding sites in synaptic endings and in intracellular membranes of rat cerebral cortex. J Biol Chem 1990, 265: 9140-9145.

[134]Teather LA, Afonso VM, Wurtman RJ. Inhibition of platelet-activating factor receptors in hippocampal plasma membranes attenuates the inflammatory nociceptive response in rats. Brain Res 2006, 1097: 230-233.

[135]Besson J, Sarrieau A, Vial M, Marie JC, Rosselin G, Rostene W. Characterization and autoradiographic distribution of vasoactive intestinal peptide binding sites in the rat central nervous system. Brain Res 1986, 398: 329-336.

[136]Aton SJ, Colwell CS, Harmar AJ, Waschek J, Herzog ED. Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons. Nat Neurosci 2005, 8: 476-483.

[137]Acsády L, Arabadzisz D, Freund TF. Correlated morphological and neurochemical features identify different subsets of vasoactive intestinal polypeptide immunoreactive interneurons in the rat hippocampus. Neuroscience 1996, 73: 299-315.

[138]Ishihara T, Shigemoto R, Mori K, Takahashi K, Nagata S. Functional expression and tissue distribution of a novel receptor for vasoactive intestinal polypeptide. Neuron 1992, 8: 811-819.

[139]Macsai M, Szabo G, Telegdy G. Vasoactive intestinal polypeptide induces analgesia and impairs the antinociceptive effect of morphine in mice. Neuropeptides 1998, 32: 557-562.

[140]Ternianov A, Kalfin R, Belcheva I. Antinociceptive effect of vasoactive intestinal peptide (VIP) microinjected into the rats CA1 hippocampal area. C R Acad Bulg Sci 2001, 54: 95-96.

[141]Belcheva I, Ivanova M, Tashev R, Belcheva S. Differential involvement of hippocampal vasoactive intestinal peptide in nociception of rats with a model of depression. 2009, Peptides (in press).

[142]Soulairac A, Gottesmann CL, Charpentier J. Effects of pain and of several analgesics on cortex, hippocampus and reticular formation of brain stem. Int J Neuropharmacol 1967, 6: 71-81.

[143]Sinnamon HM, Schwartzbaum JS. Dorsal hippocampal unit and EEG responses to rewarding and aversive brain stimulation in rats, Brain Res 1973, 56: 183-202.

[144]Archer DP, Roth SH. Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography. Br J Anaesth 1997, 79: 744-749.

[145]Heale VR, Vanderwolf CH. Dentate gyrus and olfactory bulb responses to olfactory and noxious stimulation in urethane anaesthetized rats. Brain Res 1994, 652: 235-242.

[146]Sinclair JG, Lo GF. Morphine, but not atropine, blocks nociceptor-driven activity in rat dorsal hippocampal neurones. Neurosci Lett 1986, 68: 47-50.

[147]Yang XF, Xiao Y, Xu MY. Both endogenous and exogenous ACh plays antinociceptive role in the hippocampus CA1 of rats. J Neural Transm 2008, 115: 1-6.

[148]Ben-Ari Y, Krnjević K, Reinhardt W, Ropert N. Intracellular observations on the disinhibitory action of acetylcholine in the hippocampus. Neuroscience 1981, 6: 2475-2484.

[149]Krnjeviæ K, Ropert N. Electrophysiological and pharmacological characteristics and facilitation of hippocampal population spikes by stimulation of the medial septum. Neuroscience 1982, 7: 2165-2183.

[150]Khanna S, Sinclair JG. Noxious stimuli produce prolonged changes in the CA1 region of rat hippocampus. Pain 1989, 39: 337-343.

[151]Leung LS, Yim CY. Intracellular records of theta rhythm in hippocampal CA1 cells of the rat. Brain Res 1986, 367: 323-327.

[152]Ylinen A, Soltesz I, Bragin A, Penttonen M, Sik A, Buzsaki G. Intracellular correlates of hippocampal theta rhythm in identified pyramidal cells, granule cells and basket cells. Hippocampus 1995, 5: 78-90.

[153]Zheng F, Khanna S. Hippocampal field CA1 interneuronal nociceptive respionses modulation by medial septal region and morphine. Neuroscience 1999, 93: 45-55.

[154]Khanna S, Zheng F. Morphine reversed formalin-induced CA1 pyramidal cell suppression via an effect on septohippocampal neural processing. Neuroscience 1999, 89: 61-71.

[155]Miller SN, Groves PM. Sensory evoked neuronal activity in the hippocampus before and after lesions of the medial septal nuclei. Physiol Behav 1977, 18: 141-146.

[156]Bland BH. The physiology and pharmacology of hippocampal formation theta rhythms. Prog Neurobiol 1986, 26: 1-54.

[157]Behrends JC, Ten Bruggencate G. Cholinergic modulation of synaptic inhibition in the guinea pig hippocampus in vitro: excitation of GABAergic interneurons and inhibition of GABA-release. J Neurophysiol 1993, 69: 626-629.

[158]Khanna S. Nociceptive processing in the hippocampus and entorhinal cortex, neurophysiology and pharmacology. In: Schmidt RF, Willis WD Ed. Encyclopedia of Pain. Berlin: Springer-Verlag, 2007, 1369-1374.

[159]Mody I, Pearce RA. Diversity of inhibitory neurotransmission through $GABA_A$ receptors. Trends Neurosci 2004, 27: 569-575.

[160]Tai SK, Huang FD, Moochhala S, Khanna S. Hippocampal theta state in relation to formalin nociception. Pain 2006, 121: 29-

42.

[161]Ko S, Zhuo M. Central plasticity and persistent pain. Drug Discov Today 2004, 1: 101-106.

[162]Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000, 288: 1765-1768.

[163]Zhuo M. Targeting central plasticity: a new direction of finding painkillers. Curr Pharm Des 2005, 11: 2797-2807.

[164]Zhuo M. Cortical excitation and chronic pain. Trends Neurosci 2008, 31: 199-207.

[165]Wei F, Xu ZC, Qu Z, Milbrandt J, Zhuo M. Role of EGR1 in hippocampal synaptic enhancement induced by tetanic stimulation and amputation. J Cell Biol 2000, 149: 1325-1333.

[166]Chen J. The bee venom test: a novel useful animal model for study of spinal coding and processing of pathological pain information. In: Chen J, Chen CAN, Han JS, Willis WD Ed. Experimental Pathological Pain: from Molecules to Brain Function. Beijing: Science Press, 2003, 77-110.

[167]Chen J. Processing of different 'phenotypes' of pain by different spinal signaling pathways. In: Kumamoto K Ed. Cellular and molecular mechanisms for the modulation of nociceptive transmission in the peripheral and central nervous system. Recent Research Development Series, Kerala: Research SignPost, 2007, 147-165.

[168]Chen J, Luo C, Li HL, Chen HS. Primary hyperalgesia to mechanical and heat stimuli following subcutaneous bee venom injection into the plantar surface of hindpaw in the conscious rat: a comparative study with the formalin test. Pain 1999, 83: 67-76.

[169]Chen YN, Li KC, Li Z, Shang GW, Liu DN, Lu ZM *et al*. Effects of bee venom peptidergic components on rat pain-related behaviors and inflammation. Neuroscience 2006, 138: 631-640.

[170]Chen HS, Chen J. Secondary heat, but not mechanical, hyperalgesia induced by subcutaneous injection of bee venom in the conscious rat: effect of systemic MK-801, a non-competitive NMDA receptor antagonist. Eur J Pain 2000, 4: 389-401.

[171]Lariviere WR, Melzack R. The bee venom test: a new tonic-pain test. Pain 1996, 66: 271-277.

[172]Pennypacker KR, Hong JS, McMillian MK. Implications of prolonged expression of Fos-related antigens. Trends Pharmacol Sci 1995, 16: 317-321.

[173]Zimmermann M, Herdegen T. Control of gene transcription by Jun and Fos proteins in the nervous system. Beneficial or harmful molecular mechanisms of neuronal responses to noxious stimulation? Am Pain Soc J 1994, 3: 33-48.

[174]Chang Y, Yan LH, Zhang FK, Gong KR, Liu MG, Xiao Y *et al*. Spatiotemporal characteristics of pain-associated neuronal activities in primary somatosensory cortex induced by peripheral persistent nociception. Neurosci Lett 2008, 448: 134-138.

[175]Harris JA. Using c-fos as a neural marker of pain. Brain Res Bull 1998, 45: 1-8.

[176]Herrera DG, Robertson HA. Activation of c-fos in the brain. Prog Neurobiol 1996, 50: 83-107.

[177]Aloisi AM, Zimmermann M, Herdegen T. Sex-dependent effects of formalin and restraint on c-Fos expression in the septum and hippocampus of the rat. Neuroscience 1997, 81: 951-958.

[178]Aloisi AM, Ceccarelli I, Herdegen T. Gonadectomy and persistent pain differently affect hippocampal c-Fos expression in male and female rats. Neurosci Lett 2000, 281: 29-32.

[179]Ceccarelli I, Scaramuzzino A, Aloisi AM. Effects of formalin pain on hippocampal c-Fos expression in male and female rats. Pharmacol Biochem Behav 1999, 64: 797-802.

[180]Pearse D, Mirza A, Leah J. Jun, Fos and Krox in the hippocampus after noxious stimulation: simultaneous-input-dependent expression and nuclear speckling. Brain Res 2001, 894: 193-208.

[181]Funahashi M, He YF, Sugimoto T, Matsuo R. Noxious tooth pulp stimulation suppresses c-fos expression in the rat hippocampal formation. Brain Res 1999, 827: 215-220.

[182]Milbrandt J. A nerve growth factor-induced gene encodes a possible transcriptional regulatory factor. Science 1987, 238: 797-799.

[183]Malcangio M, Lessmann V. A common thread for pain and memory synapses? Brain-derived neurotrophic factor and trkB receptors. Trends Pharmacol Sci 2003, 24: 116-121.

[184]Vaught JL. Substance P antagonists and analgesia: A review of the hypothesis. Life Sci 1988, 43: 1419-1431.

[185]Hunt SP, Mantyh PW. The molecular dynamics of pain control. Nat Rev Neurosci 2001, 2: 83-91.

[186]McCarson KE, Krause JE. NK-1 and NK-3 type tachykinin receptor mRNA expression in the rat spinal cord dorsal horn is increased during adjuvant or formalin-induced nociception. J Neurosci 1994, 14: 712-720.

[187]Zhou XF, Rush RA. Endogenous brain-derived neurotrophic factor ical excitation and chronic pain. Neuroscience 1996, 74: 945-953.

[188]Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, *et al*. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 1998, 281: 1640-1645.

[189]McLean S. Do substance P and the NK1 receptor have a role in depression and anxiety? Curr Pharm Des 2005, 11: 1529-1547.

[190]Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995, 15: 7539-7547.

[191]Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. Brain Res 1992, 588: 341-345.

[192]Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 1998, 95: 3168-3171.

[193]Kim JJ, Diamond DM. The stressed hippocampus, synaptic plasticity and lost memories. Nat Rev Neurosci 2002, 3: 453-462.

[194]McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci 1999, 22: 105-122.

[195]Duric V, McCarson KE. Effects of analgesic or antidepressant drugs on pain- or stress-evoked hippocampal and spinal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression in the rat. J Pharmacol Exp Ther 2006, 319: 1235-1243.

[196]Duric V, McCarson KE. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. J Pain 2006, 7: 544-555.

[197]Gould E, Tanapat P. Stress and hippocampal neurogenesis. Biol Psychiatry 1999, 46: 1472-1479.

[198]Jalalvand E, Javan M, Haeri-Rohani A, Ahmadiani A. Stress- and non-stress-mediated mechanisms are involved in pain-induced apoptosis in hippocampus and dorsal lumbar spinal cord in rats. Neuroscience 2008, 157: 446-452.

[199]Widmann C, Gibson S, Jarpe MB, Johnson GL. Mitogen-activated protein kinase: conservation of a three-kinase module from yeast to human. Physiol Rev 1999, 79: 143-180.

[200]Hodge C, Liao J, Slofega M, Guan K, Carter-Su C, Schwartz J. Growth hormone stimulates phosphorylation and activation of elk-1 and expression of c-fos, egr-1, and junB through activation of extracellular signal-regulated kinases 1 and 2. J Biol Chem 1998, 273: 31327-31336.

[201]Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. The MAPK cascade is required for mammalian associative learning. Nat Neurosci 1998, 1: 602-609.

[202]Wang X, Martindale JL, Liu Y, Holbrook NJ. The cellular response to oxidative stress: influences of mitogen-activated protein kinase signaling pathways on cell survival. Biochem J 1998, 333: 230-291.

[203]Winder DG, Martin KC, Muzzio RA, Rohrer D, Chruscinski A, Kobilka B *et al*. ERK plays a regulatory role in induction of LTP by theta frequency stimulation and its modulation by β-adrenergic receptors. Neuron 1999, 24: 715-726.

[204]Dai Y, Iwata K, Fukuoka T, Kondo E, Tokunaga A, Yamanaka H *et al*. Phosphorylation of extracellular signal-regulated kinase in primary afferent neurons by noxious stimuli and its involvement in peripheral sensitization. J Neurosci 2002, 22: 7737-7745.

[205]Ji RR. Mitogen-activated protein kinases as potential targets for pain killers. Curr Opin Investig Drugs 2004, 5: 71-75.

[206]Ji RR, Baba H, Brenner GJ, Woolf CJ. Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity. Nat Neurosci 1999, 2: 1114- 1119.

[207]Ji RR, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiol Dis 2001, 8: 1-10.

[208]Obata K, Yamanaka H, Tachibana T, Fukuoka T, Tokunaga A, Yoshikawa H *et al*. Differential activation of extracellular signal-regulated protein kinase in primary afferent neurons regulates brain-derived neurotrophic factor expression after peripheral inflammation and nerve injury. J Neurosci 2003, 23: 4117-4126.

[209]Cao FL, Liu MG, Hao J, Li Z, Lu ZM, Chen J. Different roles of spinal p38 and c-Jun N-terminal kinase pathways in bee venom-induced multiple pain-related behaviors. Neurosci Lett 2007, 427: 50-54.

[210]Cui XY, Dai Y, Wang SL, Yamanaka H, Kobayashi K, Obata K *et al*. Differential activation of p38 and extracellular signal-regulated kinase in spinal cord in a model of bee venom-induced inflammation and hyperalgesia. Mol Pain 2008, 4: 17.

[211]Guo SW, Liu MG, Long YL, Ren LY, Lu ZM, Yu HY *et al*. Region- or state-related differences in expression and activation of extracellular signal-regulated kinases (ERKs) in naïve and pain-experiencing rats. BMC Neuroscience 2007, 8: 53.

[212]Hao J, Liu MG, Yu YQ, Cao FL, Li Z, Lu ZM *et al*. Roles of peripheral mitogen-activated protein kinases in melittin-induced nociception and hyperalgesia. Neuroscience 2008, 152: 1067-1075.

[213]Li MM, Yu YQ, Fu H, Xie F, Xu LX, Chen J. Extracellular signaling-regulated kinases mediate the melittin-induced hypersensitivity of spinal neurons to chemical and thermal but not mechanical stimuli. Brain Res Bull 2008, 77: 227-232.

[214]Liu MG, Zhang FK, Guo SW, Zhao LF, An YY, Cui XY *et al*. Phosphorylation of c-Jun N-terminal kinase isoforms and their different roles in spinal cord dorsal horn and primary somatosensory cortex. Neurosci Lett 2007, 427: 39-43.

[215]Yu YQ, Chen J. Activation of spinal extracellular signaling-regulated kinases by intraplantar melittin injection. Neurosci Lett 2005, 381: 194-198.

[216]Yu YQ, Zhao F, Chen J. Activation of ERK1/2 in the primary injury site is required to maintain melittin-enhanced wind-up of rat spinal wide-dynamic-range neurons. Neurosci Lett 2009, 459: 137-141.

[217]Klamt JG, Prado WA. Antinociception and behavioral changes induced by carbachol microinjected into identified sites of the rat brain. Brain Res 1991, 549: 9-18.

[218]Aloisi AM, Alnonetti ME, Lodi L, Lupo C, Carli G. Decrease of hippocampal choline acetyltransferase activity induced by for-

malin pain. Brain Res 1993, 629: 167-170.

[219]Aloisi AM, Alnonetti ME, Carli G. Formalin-induced changes in adrenocorticotropic hormone and corticosterone plasma levels and hippocampal choline acetyltransferase activity in male and female rats. Neuroscience 1996, 74: 1019-1024.

[220]Ceccarelli I, Casamenti F, Massafra C, Pepeu G, Scali C, Aloisi AM. Effects of novelty and pain on behavior and hippocampal extracellular ACh levels in male and female rats. Brain Res 1999, 815: 169-176.

[221]McMahon SB, Koltzenburg M. Wall and Melzack's textbook of pain. Oxford, UK: Elsevier Ltd., Churchill Livingstone, 2005.

[222]Shih YY, Chen YY, Chen CC, Chen JC, Chang C, Jaw FS. Whole-brain functional magnetic resonance imaging mapping of acute nociceptive responses induced by formalin in rats using atlas registration-based event-related analysis. J Neurosci Res 2008, 86: 1801-1811.

[223]Shih YY, Chiang YC, Chen JC, Huang CH, Chen YY, Liu RS *et al*. Brain nociceptive imaging in rats using (18)f-fluorodeoxyglucose small-animal positron emission tomography. Neuroscience 2008, 155: 1221-1226.

[224]Sakiyama Y, Sato A, Senda M, Ishiwata K, Toyama H, Schmidt RF. Positron emission tomography reveals changes in global and regional cerebral blood flow during noxious stimulation of normal and inflamed elbow joints in anesthetized cats. Exp Brain Res 1998, 118: 439-446.

[225]Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005, 9: 463-484.

[226]Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 2000, 30: 263-288.

[227]Schneider F, Habel U, Holthusen H, Kessler C, Posse S, Müller-Gärtner HW *et al*. Subjective ratings of pain correlate with subcortical-limbic blood flow: an fMRI study. Neuropsychobiology 2001, 43: 175-185.

[228]Bingel U, Quante M, Knab R, Bromm B, Weiller C, Büchel C. Subcortical structures involved in pain processing: evidence from single-trial fMRI. Pain 2002, 99: 313-321.

[229]Ploghaus A, Narain C, Beckmann CF, Clare S, Bantick S, Wise R *et al*. Exacerbation of pain by anxiety is associated with activity in a hippocampus network. J Neurosci 2001, 21: 9896-9903.

[230]Derbyshire SWG, Jones AKP, Gyulai F, Clark S, Townsend D, Firestone LL. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 1997, 73: 431-445.

[231]Hsieh JC, Ståhle-Bäckdahl M, Hägermark Ö, Stone-Elander S, Rosenquist G, Ingvar M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain 1995, 64: 303-314.

[232]Peyron R, Garcý´a-Larrea L, Gre´goire MC, Costes N, Convers P, Lavenne F *et al*. Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. Brain 1999, 122: 1765-1779.

[233]LaMotte RH, Lundberg LE, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. J Physiol 1992, 448: 749-764.

[234]Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia after intradermal injection of capsaicin. Pain 1989, 38: 99-107.

[235]Iadarola MJ, Berman KF, Zeffiro TA, Byas-Smith MG, Gracely RH, Max MB *et al*. Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. Brain 1998, 121: 931-947.

[236]Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. Pain 1989, 39: 345-352.

[237]Siedenberg R, Treede RD. Laser-evoked potentials: exogenous and endogenous components. Electroencephalogr Clin Neurophysiol 1996, 100: 240-249.

[238]Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JNP, Matthews PM. Learning about pain: the neural substrate of the prediction error for aversive events. Proc Natl Acad Sci 2000, 97: 9281-9286.

[239]Mackintosh NJ. A theory of attention: variations in the associability of stimuli with reinforcement. Psychol Rev 1975, 82: 276-298.

[240]Recorla RA, Wagner AR. A theory of Pavlovian conditioning: variations in the efectiveness of reinforcement and nonreinforcement. In: Black AH, Proskasy WF Ed. Classical conditioning II: current research and theory. New York: Appleton-Century-Crofts, 1972, 64-99.

[241]Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002, 125: 310-319.

[242]Grachev ID, Fredickson BE, Apkarian AV. Dissociating anxiety from pain: mapping the neuronal marker N-acetyl aspartate to perception distinguishes closely interrelated characteristics of chronic pain. Mol Psychiatry 2001, 6: 256-260.

[243]Al Absi M, Rokke PD. Can anxiety help us tolerate pain? Pain 1991, 46: 43-51.

[244]Weisenberg M, Aviram O, Wolf Y, Raphaeli N. Relevant and irrelevant anxiety in the reaction to pain. Pain 1984, 20: 371-383.

[245]Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain 2000, 84: 65-75.

[246]Derbyshire SWG, Jones AKP, Collins M, Feinmann C, Harris M.

Cerebral responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography (PET). Eur J Pain 1999, 3: 103-113.
[247]Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and managements. Lancet 1999, 353: 1959-1964.
[248]Petrovic P, Ingvar M, Stone-Elander S, Petersson KM, Hansson P. A PET activation study of dynamic mechanical allodynia in patients with mononeuropathy. Pain 1999, 83: 459-470.
[249]Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RSJ, Frith CD *et al*. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. Ann Intern Med 1996, 124: 939-949.
[250]Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2001, 2: 51-61.
[251]Moser MB, Moser EI. Functional differentiation in the hippocampus. Hippocampus 1998, 8: 608-619.
[252]Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993, 361: 31-39.
[253]Bennett MR. The concept of long term potentiation of transmission at synapses. Prog Neurobiol 2000, 60: 109-137.
[254]Malenka RC, Nicoll RA. LTP-A decade of progress? Science 1999, 85: 1870-1874.
[255]Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP do pain and memory share similar mechanisms. Trends Neurosci 2003, 26: 696-705.
[256]Ikeda H, Heinke B, Ruscheweyh R, Sandkühler J. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. Science 2003, 299: 1237-1240.
[257]Sandkühler J. Understanding LTP in pain pathways. Mol Pain 2007, 3: 9.
[258]Heusler P, Boehmer G. Platelet-activating factor contributes to the induction of long-term potentiation in the rat somatosensory cortex in vitro. Brain Res 2007, 1135: 85-91.
[259]Wei F, Qiu CS, Liauw J, Robinson DA, Ho N, Chatila T *et al*. Calcium–calmodulin-dependent protein kinase IV is required for fear memory. Nat Neurosci 2002, 5: 573-579.
[260]Ko S, Zhao MG, Toyoda H, Qiu CS, Zhuo M. Altered behavioral responses to noxious stimuli and fear in glutamate receptor 5 (GluR5)- or GluR6-deficient mice. J Neurosci 2005, 25: 977-984.
[261]Zhao MG, Toyoda H, Lee YS, Wu LJ, Ko SW, Zhang XH *et al*. Roles of NMDA NR2B subtype receptor in prefrontal long-term potentiation and contextual fear memory. Neuron 2005, 47: 859-872.
[262]Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol 2009, 87: 81-97.
[263]May A. Chronic pain may change the structure of the brain. Pain 2008, 137: 7-15.
[264]Edwards L, Pearce S, Collett BJ, Pugh R. Selective memory for sensory and affective information in chronic pain and depression. Br J Clin Psychol 1992, 31: 239-248.
[265]Pauli P, Alpers GW. Memory bias in patients with hypochondriasis and somatoform pain disorder. J Psychosom Res 2002, 52: 45-53.
[266]Pearce SA, Isherwood S, Hrouda D, Richardson PH, Erskine A, Skinner J. Memory and pain: tests of mood congruity and state dependent learning in experimentally induced and clinical pain. Pain 1990, 43: 187-193.

海马结构在疼痛信息处理中的作用

刘明刚[1]，陈军[1,2]

[1]首都医科大学疼痛生物医学研究所，北京 100069；
[2]第四军医大学附属唐都医院疼痛生物医学研究所，西安 710038

摘要：众所周知，疼痛是一种复杂的体验与经历，包括感觉识辨、情绪动机和认知评价三个主要组成部分。近年来，人们已经逐渐认识到外周传来的伤害性信息是由脑内一个广泛存在的、阶梯分明的神经元网络(也可称为疼痛基质)完成的。因此，鉴定出这些负责疼痛各功能要素的多级神经元网络，并利用所获知识更好地治疗疼痛，已经成为摆在人们面前的艰巨任务。虽然关于痛刺激或者临床痛激发的皮层反应相关研究已经很多，但是对海马结构在痛觉处理中的作用仍存在分歧。在这里，我们整合了前人在动物和人的海马与痛的关系方面的研究工作，依次提供解剖学、行为学、电生理学、分子生物学或生物化学及功能成像方面的证据，证明海马结构与痛觉信息处理的相关性。最后，简单阐述痛与记忆之间的关系，并提出尚未解决的问题，以指导将来的研究。

关键词：痛；海马结构；解剖；行为；电生理；功能成像