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The hippocampo-prefrontal pathway: a possible therapeutic target for negative and cognitive symptoms of schizophrenia

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Abstract

The hippocampo-prefrontal (H-PFC) pathway has been linked to cognitive and emotional disturbances in several psychiatric disorders including schizophrenia. Preclinical evidence from the NMDA receptor antagonism rodent model of schizophrenia shows severe pathology selective to the H-PFC pathway. It is speculated that there is an increased excitatory drive from the hippocampus to the prefrontal cortex due to dysfunctions in the H-PFC plasticity, which may serve as the basis for the behavioral consequences observed in this rodent model. Thus, the H-PFC pathway is currently emerging as a promising therapeutic target for the negative and cognitive symptom clusters of schizophrenia. Here, we have reviewed the physiological, pharmacological and functional characteristics of the H-PFC pathway and we propose that allosteric activation of glutamatergic and cholinergic neurotransmission can serve as a plausible therapeutic approach.

Keywords

hippocampus; NMDA antagonist; plasticity; prefrontal cortex; schizophrenia

The prefrontal cortex (PFC) is considered to be the seat for several higher order cognitive functions. It is also considered as one of the key brain areas that are involved in the pathophysiology of several neurological disorders including schizophrenia. Among the diverse inputs to the PFC, afferents from the hippocampus account for a majority of its innervation. The hippocampus projects profusely to the entire PFC via a strong monosynaptic glutamatergic projection. Although the hippocampus can also influence the PFC via several indirect and polysynaptic pathways, the monosynaptic projections are hypothesized to exert a primary influence on the PFC neurons. These monosynaptic projections from the hippocampus to the PFC, which are termed as the hippocampo-prefrontal (H-PFC) pathway, has been the subject for several studies that implicate its importance in various cognitive functions. Moreover, there is growing evidence that the H-

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PFC pathway could serve as the common link for the cognitive and emotional dysfunctions in several psychiatric and neurological disorders [1].

One such chronic, debilitating psychiatric disorder is schizophrenia that is characterized by psychotic or positive symptoms, as well as negative symptoms (avolition, affective flattening, social withdrawal) and cognitive disturbances. Current antipsychotic drugs act by blocking dopamine (DA) and other monoamine receptors and reduce positive symptoms but have little efficacy in reducing negative symptoms and cognitive dysfunction. Negative and cognitive symptoms have a major negative impact on patient quality of life, and represent an urgent unmet clinical need [2]. Recently, preclinical and clinical evidence demonstrates, deficits in the interplay between the hippocampus and the PFC in schizophrenia. Given the role of the H-PFC pathway in executive function and emotional regulation, it is possible that the H-PFC pathway can have a major role in the negative and cognitive symptoms and thereby can serve as a promising therapeutic target for schizophrenia.

Here, we have reviewed the anatomical, physiological and functional characteristics of the rodent H-PFC pathway with a special emphasis on the chemical regulation of this pathway. We have lso reviewed the current pre-clinical evidence that indicates the role of the H-PFC pathway in the cognitive and negative symptoms of schizophrenia.

Anatomy & physiology of the rodent H-PFC pathway

The rodent PFC is deeply innervated by the hippocampus. There are several polysynaptic pathways by which the hippocampus can influence the rodent PFC, but there also exists a strong unidirectional monosynaptic projection from the hippocampal formation to the PFC including the medial division of the PFC. Anterograde tracer studies using Phaseolus vulgaris-leucoag-glutinin showed that the projections arise from restricted portions of the CA1 (excluding dorsal CA1) of the hippocampus and the subiculum, project via the fimbria-fornix and terminate ipsilaterally [3] in the medial as well as orbital PFC of rats [4]. Projections from the ventral hippocampus/ subiculum were the strongest, while significant projections from the intermediate CA1 area were also found [5,6]. Within the medial PFC, the prelimbic, infralimbic and cingulate areas receive abundant innervation from the H-PFC pathway, which terminates in all cortical layers. Interestingly, there is a marked difference in terminal distribution along the dorsoventral extent of the PFC, with more dense fibers in the ventral areas. In the dorsal areas, the innervation is primarily located in the deeper layers [4]. Besides the medial PFC, another significant projection primarily from the intermediate hippocampal formation to the lateral PFC was also delineated [7]. Interestingly, there is no direct projection from the PFC back to the hippocampus, instead the PFC is known to communicate with the hippocampus via the nucleus reuniens of the midline thalamus [8].

Projections from the H-PFC pathways are known to terminate in both inhibitory interneurons as well as excitatory pyramidal cells. Using intracellular recordings of PFC pyramidal neurons, it was shown that single pulse stimulation of the ventral hippocampus can lead to fixed latency excitatory post synaptic potentials (EPSPs), followed by a prolonged inhibitory post-synaptic potential (IPSP). The presence of fixed latency responses was indicative of the fact that the responses were of monosynaptic origin. Moreover, these

responses were seen in all three main classes of the pyramidal neurons, namely, regular spiking, nonactivating bursting and inactivating-bursting neurons [9]. The presence of the prolonged IPSP also indicated that it is possible there is simultaneous engagement of both pyramidal and nonpyramidal neurons. It was later shown, using extracellular recordings from anesthetized rats that indeed fast spiking interneurons of the prelimbic cortex respond to hippocampal stimulation. The responses in the interneurons were excitatory in nature and in accordance with the monosynaptic nature of the H-PFC pathway, had consistent latencies [10]. Based on morphological characteristics, recordings were from three types of interneurons, namely, aspiny stellate, spiny stellate and bitufted neurons and all fired action potentials in response to hippocampal stimulation. Using *in vitro* electrophysiological preparations in which the hippocampal afferents remained intact, it was demonstrated that both pyramidal neurons and fast spiking interneurons showed EPSPs following stimulation of the hippocampal afferents [11]. Finally, using simultaneous recording of the pyramidal neurons and interneurons *in vivo* it was shown that the interneurons consistently fired before the pyramidal cells after hippocampal stimulation. Therefore, monosynaptic excitation of interneurons by the H-PFC pathway could be responsible for feed-forward inhibition of the pyramidal neurons [10]. However, overall the H-PFC pathway is believed to have an excitatory influence on the PFC as low-frequency stimulation of the CA1/subicular region of anesthetized rats was shown to produce a net excitatory response evident in multiunit discharge as well as field recordings in the prelimbic area of the PFC [12]. Similar projection patterns from the hippocampus have also been reported in monkeys and humans [1,13–15].

Based on ultrastructural characteristics, it has been shown that hippocampal inputs terminate primarily in the dendritic spine heads of spiny pyramidal neurons [16,17]. On the other hand, they innervate primarily the dendritic shafts of the parvalbumin immunoreactive interneurons. Interestingly, no input to either calbindin or calretinin immunoreactive cells were observed [17]. Thus, there is evidence of a unique microstructure of the H-PFC pathway in the PFC, where hippocampal terminals make a triangular circuit with GABAergic interneurons and pyramidal neurons. This triad microcircuit may be highly involved in short- and long-term plasticity observed in this pathway and can also be the seat for dysregulation of this pathway in several neurological disorders.

Plasticity of the rodent H-PFC pathway

The H-PFC pathway has been shown to undergo both short- and long-term plasticity. Short-term paired pulse facilitation was observed in this pathway *in vivo* in anesthetized rats both in extracellular field recordings and intracellular recordings [9,18]. A subpopulation of the excitatory neurons also showed marked paired pulse depression [9]. Paired pulse facilitation (interstimulus intervals 20–100 ms) indicating a greater degree of facilitated presynaptic release was also confirmed using *in vitro* whole cell recordings using PFC slices where hippocampal afferents were preserved. The facilitation was observed in both excitatory and inhibitory cells. Interestingly, the paired pulse facilitation profile in the H-PFC pathway was very different from the cortical-PFC pathway investigated after stimulating Layer I. The facilitation observed in the H-PFC pathway was found to be higher than the cortical-PFC pathway [11]. A difference in paired pulse facilitation/inhibition was also observed based on

the region of the hippocampus stimulated in both rats and mice. While stimulating the intermediate hippocampus paired pulse inhibition was observed in smaller interstimulus intervals with a gradual transition to paired pulse facilitation with increasing interstimulus intervals up to 1000 ms [19–21]. In the ventral hippocampus–PFC afferents only paired pulse facilitation was observed that gradually decreased with increasing interstimulus intervals with no evidence of paired pulse inhibition. Moreover, stimulus intensity contributed strongly to short-term plasticity in the intermediate pathway [22], whereas, in the ventral pathway, it was solely dependent on interstimulus intervals [23]. It is speculated that the paired pulse facilitation and inhibition can be a direct correlate of the triangular microcircuit observed between GABAergic interneurons, pyramidal neurons and hippocampal terminals [24].

Both hippocampus and the PFC have been shown to play critical role in learning and memory in rodents. Recently, interactions between the PFC and hippocampus via the H-PFC pathway have been shown to be an important mechanism underlying learning and memory processes in the rodent brain. Classically, one of the key neurological basis underlying learning and memory has been synaptic plasticity including long-term potentiation (LTP) and long-term depression (LTD). Justifying its role in learning and memory, the H-PFC pathway also shows significant long-term synaptic plasticity. Long-term plasticity was first demonstrated in early 90s where, tetanic stimulation of the CA1/ subicular region in anesthetized rats induced an immediate, stable and persistent LTP of the prelimbic field potentials [18]. Using the same tetanic stimulation, similar LTP was induced in this pathway, in freely moving rats and shown to last for up to 3 days after induction [12]. High-frequency stimulation or low-frequency paired pulse stimulations, however, failed to induce LTD in freely moving rats and anesthetized rats [12,25]. However, a two-pulse burst low-frequency train could depotentiate a previously established LTP for more than 2 h after induction [25]. Long-term depression (LTD) in freely moving rats can be achieved using a stimulus train instead, where 900 stimulus trains (5 pulses at 250 Hz) applied at 1 Hz to the ventral hippocampus can lead to LTD which can be reversed by a subsequent 12 stimulus train (50 pulses at 250 Hz) at 0.1 Hz [26]. Bidirectional plasticity was also observed in the PFC slice preparations where the hippocampal afferents are preserved [11]. A theta burst pairing stimulus protocol in the hippocampal afferents produced strong LTP in the prelimbic cortex, whereas pairing action potentials and EPSPs at 3 Hz, produced strong LTD in this preparation. Evidence suggests that this LTP and LTD in the H-PFC pathway are involved in various cognitive functions in the rodents and they have been found to be disrupted in models of various neurobiological diseases. For example, extinction of fear conditioning and fear recall is dependent on potentiation of H-PFC pathway [27] and acute stress as well as chronic mild stress in rodents can lead to impaired LTP in this pathway, which in turn can be part of the underlying pathophysiology of stress [27,28]. Moreover, it was also shown that plasticity in the H-PFC pathway is ‘flexible’ or ‘compatible’, meaning LTD can be induced in the pathway after inducing LTP and *vice versa* [29]. This presence of bidirectional plasticity serves as evidence for the basis of several learning, memory and other cognitive tasks that involve the H-PFC pathway. Moreover, the ‘compatibility’ in the induction of LTP and LTD can explain the ability of PFC in preventing behavioral perseveration driven by previous history [29,30].

Pharmacology of the rodent H-PFC pathway

Following focal injection of retrograde tracer, D-[^{3}H] aspartate in the PFC which enabled labeling of hippocampal neurons, it was shown that the major neurotransmitter used in this pathway is glutamate. Moreover, microiontophoretic application of CNQX, an AMPA receptor antagonist, in PFC was able to completely block hippocampus stimulus induced PFC activity *in vivo* [5]. Thus, the monosynaptic H-PFC pathway consists of primarily excitatory glutamatergic pyramidal neurons, where stimulation of the pathway produces AMPA receptor mediated excitation in the PFC. There is contrasting evidence for a role of NMDA receptors in the H-PFC pathway. First application of D-AP5 a selective NMDA receptor antagonist only affected the excitatory response in a few cells, indicating that AMPA receptor dependent synaptic responses were predominant in the PFC [5]. Second, while some studies show a role of NMDA receptor in the plasticity of the H-PFC pathway, others have shown that NMDA receptor independent mechanisms of plasticity also exist in this pathway. In anesthetized rats, local perfusion of D-AP5 during the tetanic stimulus of the hippocampus, but not after LTP induction was able to block LTP induction of field potentials, while not having any effect on test stimulus driven responses [31].

The dopaminergic system is also known to have significant influence on the H-PFC pathway. PFC receives majority of its dopaminergic inputs from the ventral tegmental area (VTA), targeting primarily the deeper layers of the PFC [32–34]. This mesocortical DA system is known to primarily exert an inhibitory influence in the PFC [35,36], whereas, an excitatory influence in *in vitro* preparations has also been observed [37]. Reportedly, there is close proximity of the DA terminals with the hippocampal terminals in deep layers of the PFC [16], making the mesocortical system an ideal candidate for modulations of the excitatory H-PFC pathway. Moreover, *in vivo* activation of the mesocortical DA system by stimulating VTA can block the excitatory responses induced by hippocampal stimulation in anesthetized rats [38]. Interestingly, activation of the mesocortical system at a frequency that leads to DA overflow causes a long-lasting enhancement in the magnitude of H-PFC tetanic LTP *in vivo*. On the other hand, depletion of DA in the PFC via electrolytic lesion of the VTA has opposing effects. Thus, there was a significant correlation between the amount of DA level in the PFC and the magnitude of LTP in the H-PFC pathway [39]. Between the two major DA receptor subtypes, D1 plays an important role in influencing NMDA receptor-dependent LTP. Reverse microdialysis of SKF81297, a D1 receptor agonist in the PFC significantly increases the magnitude of LTP in a dose dependent manner in PFC following hippocampal stimulation. Similarly, infusion of D1 antagonist SCH23390 in PFC also blocked H-PFC LTP in a dose-dependent manner. However, blocking of D2 with sulpiride did not inhibit LTP, indicating little or no role of D2 in modulation of NMDA dependent LTP in this synapse. It was also shown, that the D1 receptor engages the c-AMP-Protein Kinase A pathway to induce its effect on the NMDA receptor dependent LTP [40]. This shows that there is a definite convergence of the mesocortical DA system and the H-PFC pathway in the PFC cortical neurons.

Like the dopaminergic influence on the H-PFC, there is also significant influence of the noradrenergic and serotonergic system on glutamatergic transmission of this pathway. In anesthetized rats, simultaneous stimulation of the ipsilateral locus coeruleus (LC) with the

tetanic stimulation of hippocampus led to an enhancement of LTP in the PFC for at least 40 min post induction of LTP. Conversely pharmacological inactivation of LC with lidocaine or noradrenergic depletion in PFC also significantly reduced the magnitude of LTP but did not completely block the induction of LTP in anesthetized or freely moving rats. On the same line, systemic administration of nisoxetine (a noradrenaline reuptake inhibitor) and clonidine (α2 adrenergic receptor agonist) augmented and partially blocked LTP in the H-PFC pathway *in vivo* [41]. There is contrasting evidence on the role of serotonin on H-PFC pathway. Acute and repeated administration of a selective serotonin reuptake inhibitor fluvoxamine was shown to increase the magnitude of PFC field responses following hippocampal stimulation after fluvoxamine treatment in anesthetized rats. Moreover, following repeated fluvoxamine administration there was hypersensitivity in the PFC responses to hippocampal stimulation intensity. Repeated administration of fluvoxamine also led to a significant augmentation of H-PFC LTP in anesthetized rats [42]. On the other hand, lesions of serotonergic neurons in the PFC via intracerebroventricular injections of 5,7-dihydroxytryptamine (5,7-DHT) also led to an augmentation of short-term paired pulse facilitation as well as LTP in the H-PFC pathway, while the basal synaptic transmission in this pathway remained unaffected [43]. It is speculated that depletion of serotonin in PFC can lead to an increased glutamate release (indicated by the increase in paired pulse facilitation) and also disinhibit 5-HT_{1A} receptor actions on NMDA receptors leading to an increase in the magnitude of LTP after hippocampal stimulation [43]. The contrasting results regarding the role of serotonin on the H-PFC pathway is interesting. It is possible increased synaptic serotonin over longer periods of time can have different effects on the H-PFC pathway as opposed to acute serotonin neurotransmission. Also, systemic dosing of fluvoxamine can affect several brain regions including the hippocampus, whereas, intracerebroventricular injections of 5,7-DHT only has local action on PFC. Thus serotonin may modulate the H-PFC pathway in the cortex differently than it does in the hippocampus.

There is also a tight cholinergic regulation of the H-PFC pathway that has been reported. The PFC receives cholinergic input from the brainstem and the basal forebrain structures. This cholinergic innervation acts especially via the muscarinic cholinergic receptors to modulate both LTP and LTD in the H-PFC pathway. A nonselective muscarinic receptor agonist pilocarpine when systemically dosed before tetanic stimulation of the hippocampus was able to potentiate the NMDA dependent form of LTP in the PFC, in urethane anesthetized animals. This potentiation of LTP following pilocarpine administration was characterized by a simultaneous increase in monoaminergic transmission, with significant decrease in DA, serotonin and noradrenaline levels [44]. Muscarinic activation in PFC was also able to potentiate low-frequency hippocampal stimulation induced LTD *in vivo*. Thus, intracerebroventricular administration of pilocarpine in the PFC was able to potentiate a sub-threshold form of LTD without affecting basal neurotransmission of the H-PFC pathway. This form of low-frequency stimulation-induced LTD *in vivo* is also known to be NMDA receptor-dependent. Interestingly, blockade of NMDA receptors before the muscarinic activation blocks pilocarpine's ability to potentiate the subthreshold form of LTD [45]. Thus, muscarinic receptors interact with the monoaminergic system as well as the glutamatergic system in the PFC to influence the H-PFC pathway. In addition, muscarinic activation alone has been shown to induce plasticity in this pathway. Using a slice

preparation for PFC where hippocampal inputs are preserved [11], bath application of the cholinergic agonist carbachol can induce LTD in the H-PFC pathway in a concentration dependent manner. A subsequent increase in paired pulse facilitation was also observed during the LTD, indicating possible presynaptic mechanisms for this form of LTD. Using various pharmacological tools, it was shown that the muscarinic subtype primarily governs this LTD, possibly with a role for M_2 muscarinic receptor subtype. This form of muscarinic LTD in the PFC is NMDA independent, as co-application of AP-5, an NMDA receptor antagonist failed to block the synaptic depression. However, co-application of nifedipine, voltage gated L-type calcium channel blocker and BAPTA, a postsynaptic calcium chelator block the muscarinic LTD. This indicates that postsynaptic elevation of calcium is also important for induction of this form of LTD [46]. Interestingly, this form of carbachol LTD was also observed in regular PFC slices when neurons from deeper layers of PFC were recorded intracellularly, while stimulating the superficial layers, which includes but is not exclusively comprised of projections from the hippocampus [47]. This indicates that cholinergic modulation, either in conjunction with the monoaminergic and glutamatergic neurotransmission or by itself can effectively modulate plasticity in the H-PFC pathway (Figure 1).

Functional relevance of the H-PFC pathway in normal & pathophysiological processes

In recent years, the functional coupling between the hippocampus and the PFC has been a subject of widespread interest due to its role in cognitive and emotional processing. The functional aspect of the H-PFC pathway is elaborately reviewed by Godsil *et al*. [1]. In short, there is evidence that links this pathway to learning and memory, fear regulation and even sleep-governing processes. In early studies, disconnection between hippocampus and PFC was used as a method to study its role in animal behavior. Since the hippocampus and the PFC connect ipsilaterally, disconnection between the two structures was possible by pharmacological inactivation or lesions of the hippocampus and contralateral PFC. Using this technique, Floresco *et al*. [48] showed the role of the H-PFC pathway in working memory. Animals with H-PFC disconnections performed poorly in a delayed win-shift radial arm maze task while not affecting their normal random foraging behavior. It was further shown that the H-PFC pathway is engaged in situations with increased cognitive demand during the working memory task [49]. There is also evidence for increased synchronous activity between the PFC and hippocampus during spatial working memory tasks [50,51]. Lesions of the ventral hippocampus disrupt cognitive flexibility in animals [52]. The role of functional interaction between the two structures in goal-oriented reward learning was evident when increased coherence was observed between the two structures when animals were at the point of choice in a Y-maze while acquiring a new learning rule [53]. Synchronized activity between the two structures was important for the animal to perform accurately in such tasks indicating a possible role of the H-PFC pathway in information transfer between hippocampus and the PFC during reward learning. The H-PFC pathway has also been shown to be involved in recognition memory. While the H-PFC disconnection spared simple novel object recognition in animals, it severely impaired the animals' ability to perform in more complex recognition tasks that involved contextual and

temporal details [54]. The H-PFC pathway along with its interactions with the amygdala has been shown to be critical for regulation of fear. Plasticity studies mentioned above have shown that fear extinction led to synaptic potentiation of the H-PFC pathway [27], indicating its role in fear extinction memory. Inactivation and H-PFC disconnections studies have also shown its importance in fear recall and fear renewal [55,56]. Finally, there is evidence of functional coupling between the hippocampus and PFC during sleep. The two structures are known to communicate heavily during slow wave sleep, while this is attenuated during rapid eye movement (REM) sleep. Interestingly, PFC neurons consistently fire after the hippocampus in sleeping animals, indicating possible directional interaction between these areas. This in turn can have implications in memory consolidation [57].

In addition to the evidence for behavioral contribution of the H-PFC pathway, there is growing evidence that several psychiatric disorders including schizophrenia can heavily affect the interaction between the two structures. Several lines of evidence suggest that plasticity in the H-PFC pathway is highly compromised in acute and chronic stress models in animals [27–28,58] directly implicating a role of the H-PFC pathway in stress regulation. There is also strong clinical evidence of involvement of the H-PFC pathway in major depression [59,60] and post traumatic stress disorders [61]. Patients with schizophrenia also show aberrant functional coupling between the hippocampus and the PFC at resting state [62], as well as during working memory tasks [63,64]. The role of the H-PFC pathway in schizophrenia is also evident in preclinical rodent models of the disease. Neurodevelopmental models of schizophrenia readily show a decreased theta-coherence between the hippocampus and the PFC [65]. NMDA receptor antagonism is an effective pharmacological model of schizophrenia that mimics positive, negative and cognitive symptoms of the disorder [66]. Acute or repeated administration of the NMDA receptor antagonists phencyclidine (PCP), MK-801 or ketamine induce a behavioral syndrome that includes several symptom clusters of the disease [2]. One advantage of this model has been its faithful representation of the negative and cognitive symptoms of schizophrenia [66,67], a current unmet clinical need for the disorder. Thus, administration of NMDA receptor antagonists in rodents produces a myriad of cognitive dysfunctions including deficits in novel object recognition [68–72], reversal learning [73–78], attentional set shifting [79,80] and attention [81–83]. Significant deficits in social interaction [84,85] and anhedonia [86,87] of rodents have also been shown, thus representing the negative symptom cluster of schizophrenia. The presence of the negative and cognitive symptom profiles in this animal model provides a unique opportunity to tease apart the pathophysiology related to these symptoms. Interestingly, multiple behavioral deficits observed in the animal model are directly or indirectly related to the functionality of the PFC. Indeed, the function of PFC is heavily compromised after treatment with NMDA receptor antagonists. Acute systemic administration of PCP or MK-801 led to a tonic excitation of PFC neurons in anesthetized as well as freely moving rats [88–91]. This increase in PFC excitability was also observed after repeated administration of PCP in rats [92]. It is possible that the glutamatergic H-PFC pathway can be a primary source for the NMDA receptor antagonist induced dysfunction of the PFC. Evidence supporting this hypothesis comes from studies that show that PCP can lead to disinhibition of the hippocampus [93]. Other studies have shown that local application of PCP or MK-801 in the rodent PFC fails to mimic the tonic excitation of PFC

neurons observed after systemic administration [91,94]. Local application of PCP even failed to elicit any detectable increase in excitatory synaptic currents of PFC neurons [95]. On the other hand, local application of PCP or MK-801 in the ventral hippocampus led to enhanced excitation of the PFC [94]. Moreover, only hippocampal neurons projecting to the PFC were disinhibited and excited and not the ones that were unconnected to the PFC [94]. Also, acute MK-801 treatment has been shown to cause a long lasting increase in PFC responses evoked by ventral hippocampus. This potentiation of PFC responses shared a common mechanism involved with high-frequency stimulation induced LTP generation in the H-PFC pathway as it occluded the generation of such LTP in this pathway. This aberrant plasticity occurred in conjunction with cognitive deficits in the animals and also decayed in parallel within 24 h after the MK-801 treatment [96,97]. A recent study also showed that following repeated administration of MK-801 in rodents there is a shift from LTD to LTP in the H-PFC pathway. However, no changes were observed in the amygdala to PFC pathway, indicating a central role of the H-PFC pathway in this animal model. In addition, a normal inhibitory regulation of the amygdala-PFC pathway by the H-PFC pathway was also disrupted following MK-801 administration [98]. All of these studies directly support the hypothesis that H-PFC pathway functionality and plasticity can be directly linked to the pathophysiology observed in PFC following NMDA receptor antagonism. Moreover, the striking similarity of the functional impact of the H-PFC pathway and the behavioral deficits observed in the NMDA receptor antagonist model of schizophrenia makes it a promising target for the negative and cognitive symptoms of schizophrenia (Figure 2).

Conclusion & future perspective

In summary, the H-PFC pathway provides a strong excitatory drive in the PFC and is subject to bidirectional short- and long-term plasticity. It is under tight chemical regulation from the glutamatergic, monoaminergic and cholinergic neurotransmission. There is also a direct correlation in the physiology and plasticity of this pathway to its functional relevance. It by means of its bidirectional plasticity is strongly involved in working memory, goal oriented learning, fear regulation and sleep (Figure 1). Thus, much is now known about the characteristics and functional relevance of the H-PFC pathway but a number of unanswered questions remain. For example, PFC has high expression of metabotropic glutamate receptors (mGluR) including the subtypes $mGlu_2$, $mGluR_3$ and $mGluR_5$, each of which is being investigated as a potential target for treatment of schizophrenia and other disorders that include disruptions in PFC function. Surprisingly, little is known regarding the role of mGluRs in regulating the glutamatergic projections from the hippocampus. $mGluR_5$, being a strong signaling partner of NMDA receptors [99–102] has the potential to exert a strong influence on the H-PFC pathway. Also, the group II mGluRs may regulate transmission at this excitatory synapse. Similarly, although it is known that muscarinic receptors are involved in long-term plasticity in this pathway, important information regarding the muscarinic subtype that governs such mechanisms is either missing or less convincing. Information regarding receptor subtypes is important from a drug discovery perspective as identifying subtype specific targets will enable reducing the risk of adverse effects. One of the challenges in the past has been the lack pharmacological tools to address such questions. Moreover, the long range of the H-PFC pathway, makes it a difficult target to study, where

researchers have to rely on extremely difficult *in vivo* techniques to characterize this pathway. However, recently with the advent of several important pharmacological tools, such as selective $mGlu_5$, $mGlu_{2/3}$, M_1 and M_4 modulators [103–108] as well as optogenetic techniques to reliably and selectively study long-range projections, makes it an exciting time to revisit the H-PFC pathway.

The importance of the H-PFC pathway in schizophrenia has also been apparent. From clinical evidence in schizophrenic patients to strong preclinical indications, the H-PFC pathway is slowly emerging as one of the therapeutic targets for the negative and cognitive symptoms of schizophrenia. The pharmacological rodent model that relies on NMDA receptor antagonism provides reliable face, construct and predictive validity for schizophrenia. Although not devoid of drawbacks it is still considered as a fantastic tool to study therapeutic efficacy in the different symptom clusters of schizophrenia [2,66,109]. The existence of such a model makes it a relatively easier task to further tease apart the role of the H-PFC pathway in the negative and cognitive symptom clusters. The increased excitatory drive of the PFC from the hippocampus and a shift in balance in H-PFC plasticity in favor of LTP provide strong evidence for the involvement of this pathway in NMDA receptor antagonism model of schizophrenia. Given the varied and tight pharmacological regulation of the plasticity in this pathway, there are several avenues by which the disrupted balance between LTP and LTD can be restored. For example, developing agents that modify cholinergic and glutamatergic neurotransmission in the PFC can help to reverse the pathophysiology in this pathway following NMDA receptor antagonism. Indeed, it has been shown that applying LY379268 a group II mGluR agonist can normalize PCP induced excessive release of glutamate [110]. However, developing direct agonists or antagonists as potential drug candidates has its disadvantages due to its adverse effect liabilities. Also, they severely lack subtype selectivity and thus it is impossible to tease apart the role of each subtype. Instead, allosteric modulators are one class of compounds that can serve as effective candidates for such a purpose. Allosteric modulators are compounds that do not bind to the orthosteric ligand binding site of the receptors, but instead bind and act on other sites to either potentiate activation of the receptors by its natural ligand (positive allosteric modulator or PAMs) or negatively modulate the receptor activation following binding of the natural ligand (negative allosteric modulators or NAMs) [111]. Such modulators have the potential to be extremely subtype selective due to less conservation of allosteric sites between subtypes as compared with orthosteric sites. The subtype selectivity combined with a lack of direct activation of receptors makes them favorable drug candidates over direct agonists and antagonists [112]. Thus, positive allosteric modulation of $mGluR_5$ may serve in potentially promoting NMDA dependent LTD and thereby restoring the balance between LTP and LTD. In line with this hypothesis, there are already emerging reports that $mGluR_5$ PAMs can reverse cognitive deficits in object recognition following ketamine administration [68]. Similarly, allosteric activation of muscarinic receptors can promote LTD in PFC and restore normal excitatory drive in the H-PFC pathway. Supporting the hypothesis, it is shown that BQCA, an M_1 PAM was able to enhance muscarinic LTD in the PFC [47]. Whether, such allosteric modulators of the cholinergic neurotransmission can be potentially promising candidates in ameliorating the H-PFC dysfunctions following NMDA receptor hypofunction, remains to be seen (Figure 2).

Thus, in conclusion the H-PFC pathway has immense functional relevance that is evident even in rodents. Moreover, preclinical evidence from the NMDA receptor antagonism model heavily implicates its role in the negative and cognitive symptoms clusters of schizophrenia. Therefore, designing and optimizing drugs and compounds that show efficacy in modulating the H-PFC pathway will be a promising approach to counter the negative and cognitive symptom cluster of schizophrenia.

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EXECUTIVE SUMMARY

Anatomy & physiology of the rodent hippocampo-prefrontal (H-PFC) pathway

- The intermediate and ventral hippocampus projects monosynaptically to the medial as well as orbital prefrontal cortex (PFC). The projections span all layers of the PFC and innervate both excitatory and inhibitory neurons.

Plasticity of the rodent H-PFC pathway

- The H-PFC pathway shows both short- and long-term plasticity. Paired pulse facilitation and depression as well as LTP and LTD are observed in this pathway. Long-term plasticity in this pathway is bidirectional as well as compatible and is relevant for several functions served by this pathway.

Pharmacology of the rodent H-PFC pathway

- The monosynaptic connections of the H-PFC pathway are primarily glutamatergic in nature, and synaptic responses are mediated primarily by AMPA receptors with modulation from the *N*-methyl-D-aspartate (NMDA) receptors. There is presence of both NMDA receptor-dependent and NMDA receptor-independent forms of plasticity in this pathway. Both these forms of plasticity are under tight modulation from dopaminergic, serotonergic, noradrenergic as well as cholinergic neurotransmission.

Functional relevance of the H-PFC pathway in normal & pathophysiological processes

- The H-PFC pathway has been shown to be important for cognitive performance and emotional regulation in rodents. It has been shown to be important for working memory, reversal learning, goal-oriented reward learning, fear regulation and sleep. Preclinical evidence from NMDA receptor antagonism models show that there is a shift in balance between LTP and LTD in favor of LTP in the H-PFC pathway. This can underlie the increased excitatory drive observed in PFC and subsequent behavioral abnormalities following NMDA receptor antagonist administration.

Conclusion & future perspective

- The evidence from the NMDA receptor antagonism model of schizophrenia suggests that the H-PFC pathway can be heavily implicated in negative and cognitive symptoms of schizophrenia and thus can be a promising therapeutic target. We propose that modulating glutamatergic and cholinergic neurotransmission, potentially by allosteric modulators can serve as a promising therapeutic approach.

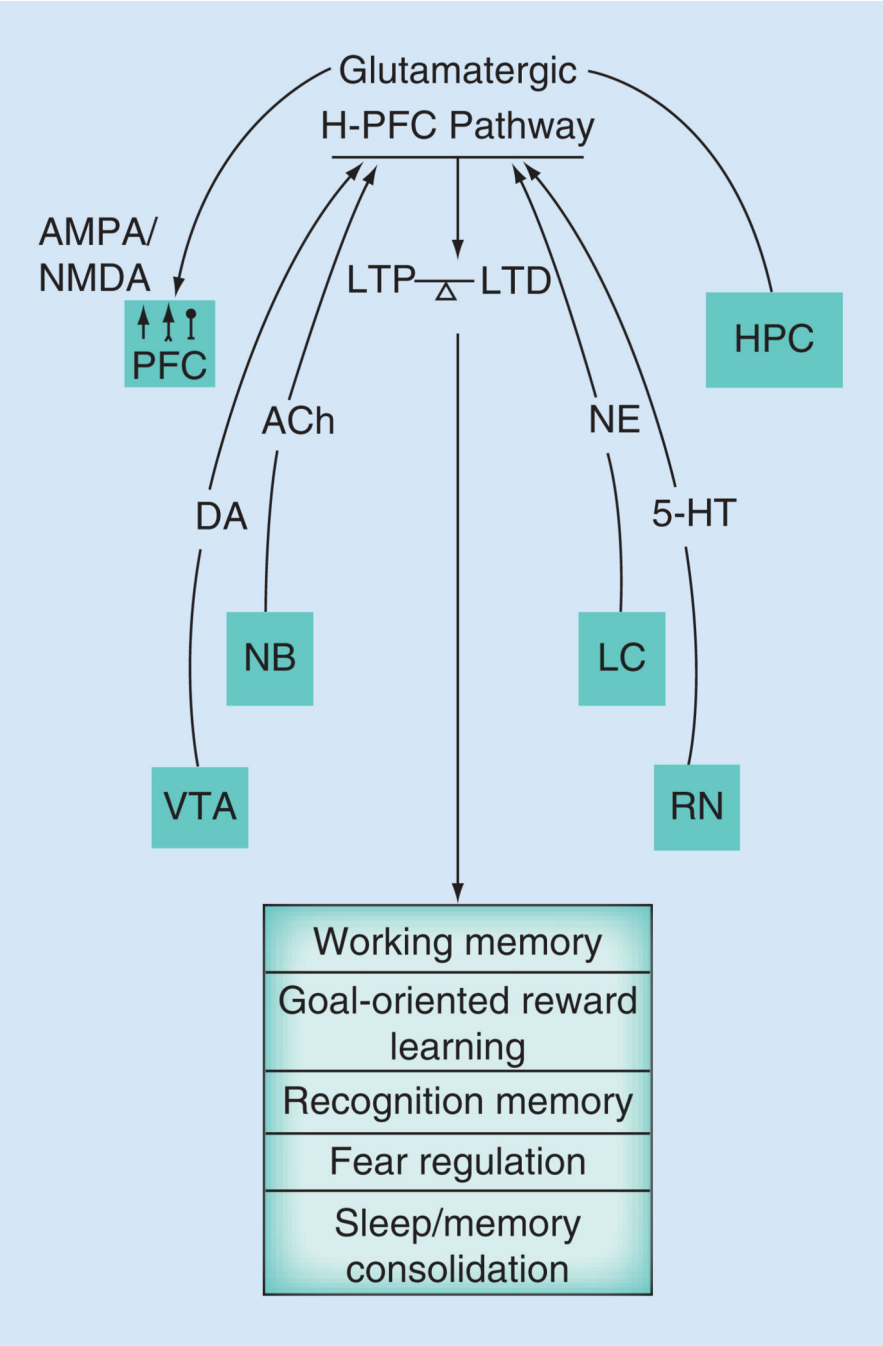

Figure 1. Characteristics of the hippocampo-prefrontal pathway

The H-PFC pathway comprises glutamatergic monosynaptic projections from the HPC to the PFC. It has an excitatory influence (↑) on both pyramidal and inhibitory interneurons in PFC via both NMDA and AMPA receptor activation. There is dopaminergic, cholinergic and monoaminergic influence on the H-PFC pathway that helps to maintain a balance between long-term potentiation and long-term depression in this pathway. This balance is thought be an important factor for the normal behavioral phenotype in rodents associated with the pathway.

5-HT: Serotonin; ACh: Acetylcholine; DA: Dopamine; H-PFC: Hippocampo-prefrontal cortex; HPC: Hippocampus; LC: Locus coeruleus; NB: Nucleus basalis; NE: Norepinephrine; PFC: Prefrontal cortex; RN: Raphe nuclei; VTA: Ventral tegmental area.

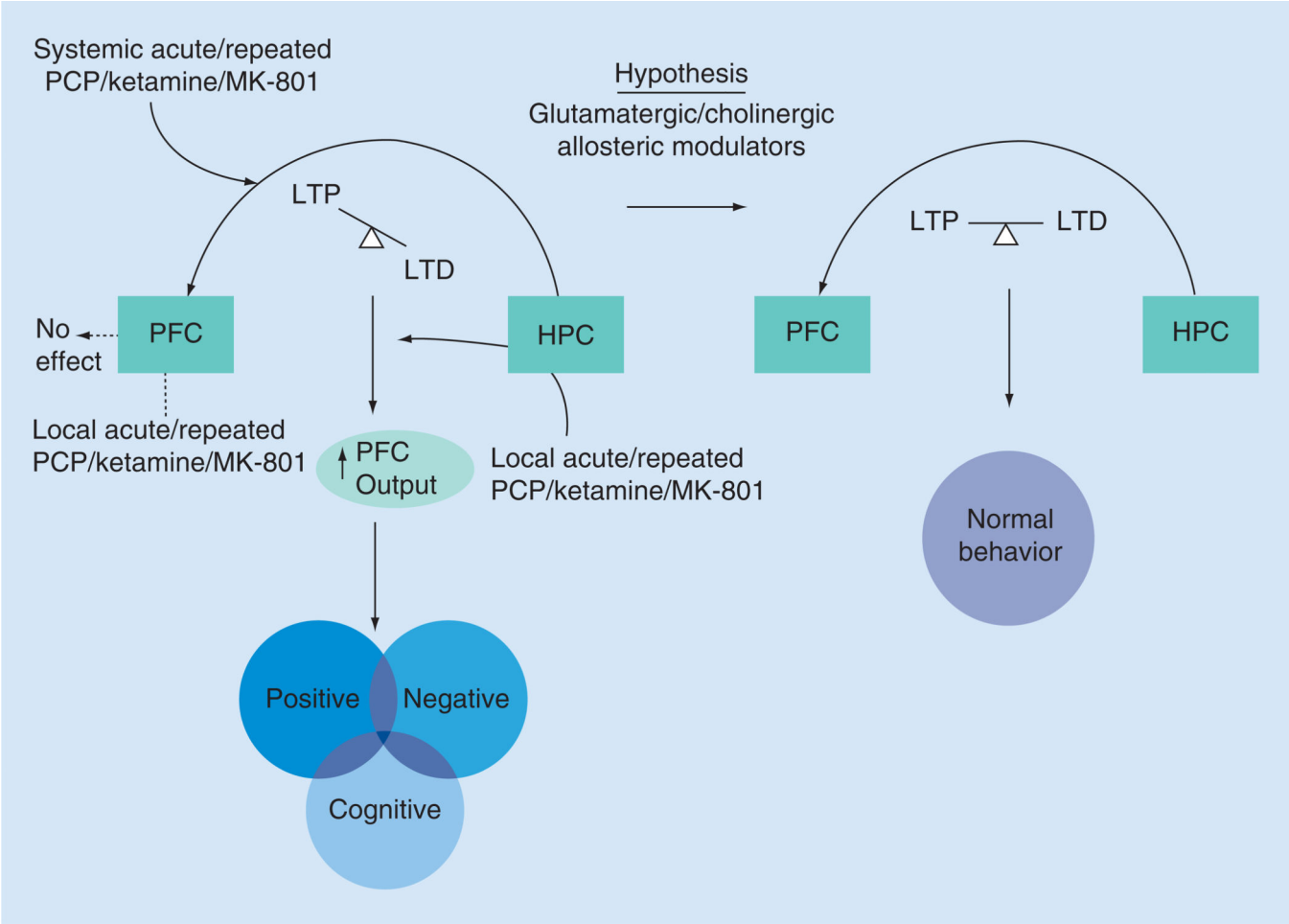

Figure 2. Pathophysiology of the hippocampo-prefrontal pathway after NMDA receptor antagonism

Systemic administration of both acute and repeated treatment or local application in the HPC of NMDA receptor antagonists leads to an excessive excitatory drive in the PFC (increased PFC output), which is lacking when they are locally infused in the PFC. This heavily implicates that NMDA receptor antagonists affect the H-PFC pathway and tilts the LTP–LTD balance in this pathway toward potentiation. This loss in LTP–LTD balance can be responsible for the increased PFC output and the behavioral phenotype observed in a NMDA receptor antagonist rodent model of schizophrenia. We hypothesize that glutamatergic and cholinergic allosteric modulators with supreme subtype selectivity will be ideal candidates to act on this pathway and restore the LTP–LTD balance and thereby rescue the behavioral abnormalities in this rodent model.

HPC: Hippocampus; LTD: Long-term depression; LTP: Long-term potentiation; PCP: Phencyclidine; PFC: Prefrontal cortex.