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TOPIC HIGHLIGHT

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Central serotonergic and noradrenergic receptors in functional dyspepsia

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Abstract

Functional dyspepsia is a symptom complex characterised by upper abdominal discomfort or pain, early satiety, motor abnormalities, abdominal bloating and nausea in the absence of organic disease. The central nervous system plays an important role in the conducting and processing of visceral signals. Alterations in brain processing of pain, perception and affective responses may be key factors in the pathogenesis of functional dyspepsia. Central serotonergic and noradrenergic receptor systems are involved in the processing of motor, sensory and secretory activities of the gastrointestinal tract. Visceral hypersensitivity is currently regarded as the mechanism responsible for both motor alterations and abdominal pain in functional dyspepsia. Some studies suggest that there are alterations in central serotonergic and noradrenergic systems which may partially explain some of the symptoms of functional dyspepsia. Alterations in the autonomic nervous system may be implicated in the motor abnormalities and increases in visceral sensitivity in these patients. Noradrenaline is the main neurotransmitter in the sympathetic nervous system and again alterations in the functioning of this system may lead to changes in motor function. Functional dyspepsia causes considerable burden on the patient and society. The pathophysiology of functional dyspepsia is not fully understood but alterations in central processing by the serotonergic and noradrenergic systems may provide plausible explanations for at least some of the symptoms and offer possible treatment targets for the future.

Key words: Functional dyspepsia; Serotonin; Noradrenaline; Gastrointestinal disorders

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INTRODUCTION

Dyspepsia is defined as pain or discomfort centred in the upper abdomen[1]. Discomfort specifically includes early satiety, fullness, upper abdominal bloating and nausea[2]. It is a common symptom and comprises 30 to 40% of all abdominal complaints presenting to gastroenterologists[3]. Patients treated in primary care usually have uninvestigated dyspepsia, and their symptoms may have an underlying structural cause, such as peptic ulcer disease, reflux oesophagitis, or endoscopy negative gastro-oesophageal reflux disease. However, a large number of these patients will have functional dyspepsia (FD) where there is no structural or biochemical explanation for their symptoms following appropriate investigation[3].

FD may be categorised by the predominant symptom into ulcer-like, dysmotility-like, and unspecified dyspepsia. Ulcer-like dyspepsia has pain as the predominant symptom while dysmotility-like dyspepsia has predominantly discomfort. There was another category of dyspepsia, reflux-like dyspepsia, but this is no longer included as these patients have reflux disease and are treated as such. This classification scheme was first used as an aid in the design and performance of clinical trials. Its clinical use beyond taxonomy has yet to be proven[1,2].

FD is a heterogeneous disorder which does not have a well established pathophysiology. Gastrointestinal motor abnormalities, altered visceral sensation, and psychosocial factors have all been identified as major pathophysiological mechanisms. It has become more evident recently that FD is a biopsychosocial disorder[4] in which these three major pathophysiological mechanisms interact to generate the symptoms. This view has now replaced the earlier perspective that the condition was the result of a sole motor or sensory disorder of the stomach[5]. There is much controversy whether *Helicobacter pylori* infection induces FD or not. Some studies suggest that it is implicated in a small proportion of patients with FD[6] whilst others suggest that it is not involved in the pathophysiology at all[7].

The motor, sensory and secretory activities of the

intestine occur through the coordinated bidirectional communications between the central nervous system (brainstem and cerebral cortex), the autonomic nervous system (ANS) (sympathetic and parasympathetic neuronal pathways) and the enteric nervous system[8]. These systems form what is known as the brain-gut axis[9,10]. FD symptoms may result from deregulated interactions at any level of the brain-gut axis. Recent studies emphasize the role of the central nervous system (CNS) in conducting and processing visceral signals and suggest that alterations in brain processes involving perception and affective responses might be key factors in the pathogenesis of functional gastrointestinal symptoms[10]. Familial clustering of FD has been reported[11] which suggest a genetic component. FD causes considerable burden on the affected patient and society[12].There is now evidence to support the fact that functional disorders such as FD impair the affected patients to a similar extent as a disease with well-defined structural lesions; this disorder also causes considerable loss of working time and a large financial expense for medical management[13].

There is substantial evidence to suggest that patients with FD have a higher incidence of psychological disorders than population controls[14]. Patients with unexplained gastrointestinal complaints are more likely to suffer from symptoms of neurosis, anxiety, hypochondriasis and depression than controls[15,16]. Some studies have also revealed that there are possible links between emotional factors and changes in gastrointestinal physiology which may lead to abnormal gastric secretion, gut motility and function[17].

Life stress contributes to symptom onset and exacerbation in the majority of patients with FD[18]. Acute stress affects upper gastrointestinal motility and gastric acid secretion. However, studies of acute stress in FD patients have conflicting results[19]. A longitudinal study assessed the relationship of chronic and severe life stress to subsequent symptom intensity in patients with FD. The results of this study showed that severe and chronic threat has large and consistent effects on symptom intensity over time in FD patients[18].

VISCERAL HYPERSENSITIVITY

Visceral hypersensitivity is currently regarded as the mechanism responsible for both motor alterations and abdominal pain in functional bowel disorders including FD[20]. In order to elucidate the origins of visceral hypersensitivity it is necessary to understand the neuroanatomy and physiology of visceral sensation itself. Enteroendocrine cells in the lining of the gut act as chemical and mechanical transducers for local reflexes of initiation of afferent projections to the CNS[21]. Gut afferent signals reach conscious perception through a three neuron chain[4]. The cell body of the first order neuron is in the dorsal root ganglion and this neuron terminates in the dorsal column of the spinal cord. En passant fibres project to noradrenergic neuron in the prevertebral ganglia. This reflex centre results in modulation of viscus functions such as motility. Somatic and visceral afferents converge on dorsal horn neurons and result in viscerosomatic projection or referred pain. Descending controlling fibres such as serotonergic and noradrenergic from brainstem centres alter the sensitivity of the dorsal horn neurons and therefore centrally control the intensity of perception during visceral stimulation[21].

The second order neuron projects from the dorsal horn of the spinal cord to the thalamus and reticular formation in the brainstem. The ascending pathways are found in the spinoreticular and spinothalamic tracts. Nociceptive spinal pathways have recently been identified in the dorsal column of primates. These project nociception from viscera such as pancreas, colorectum, and duodendum (the upper bowel)[22]. This was also found in studies using rats[23]. These second order neurons synapse with satiety and autonomic centres and also the third order neurons that lead to emotional responses (limbic system) and conscious perception (sensory cortex). These projections lead to alterations in pulse rate, blood pressure, appetite and emotions in response to visceral pain. The loci of projection in the sensory cortex are not fully elucidated yet[24]. At present there is a limited understanding of the cerebral processing of visceral stimuli, the pathways and mediators of visceral afferents, the role of end organ modulation of sensation and association of symptoms with sensorimotor dysfunctions. Among the neurotransmitters involved in visceral perception are serotonin and noradrenaline. Different receptor subtypes for the transmitters may also have differential effects[24].

NEUROANATOMY OF THE SEROTONIN AND NORADRENALINE SYSTEMS

Serotonin is a neurotransmitter in the CNS and in the gastrointestinal tract. There are seven known serotonergic receptors, of which 5-HT_1, 5-HT_3, 5-HT_4 receptors (and their subtypes) seem to play an important role in the gut[25]. Centrally serotonin neurons are found at most levels of the brainstem and are concentrated in the raphe nuclei. Serotonergic neurons innervate virtually all parts of the CNS. Projections from the rostral raphe nuclei reach the forebrain, providing a cortical innervation that is the densest in sensory and limbic areas. Caudal raphe nuclei provide most of the projections to the brainstem and spinal cord.

Noradrenaline systems are also located in the CNS and within the gastrointestinal tract. There are two main types of adrenoreceptors α and β. There is two of each of the receptors: α_1 and β_1 are located on the post-synaptic membrane while α_2 and β_2 are found on the pre-synaptic membrane. Noradrenergic neurons are found in the pons and the medulla of the brainstem. Most are located in an area called the locus ceruleus, a collection of pigmented cells located near the floor of the fourth ventricle. The remainder of noradrenergic neurons are found in the lateral parts of the medullary reticular formation, in some nuclei associated with cranial nerves (the solitary nucleus and the dorsal motor nucleus of the vagus). Collectively these neurons innervate nearly the entire CNS. Ascending fibres reach the thalamus, hypothalamus, limbic forebrain structures and the cerebral cortex. All areas of the cerebral cortex receive some noradrenergic innervation with

the somatosensory cortex receiving a particularly dense innervation. Descending fibres project to other parts of the brainstem and to all spinal levels as well as the cerebellum[26].

INTERACTION OF SEROTONIN AND NORADRENALINE SYSTEMS

Central serotonergic pathways have been implicated in the mechanisms of nociception. Conflicting results have been published because serotonin administered intrathecally is seen to either inhibit or stimulate nociceptive responses. This may depend on the dose and the species studied[20].

While both supraspinally and spinally projecting serotonin pathways are involved in the modulation of nociceptive transmission, it is the pathways originating in the brainstem and projecting to the dorsal horn of the spinal cord that have been studied the most. This is due to the proposal of an endogenous pain-suppressing system using serotonin[27]. The actions of serotonin depend on the receptor subtype being activated and the response may be pronociceptive or antinociceptive[28]. Activation of spinal 5-HT_{1B} and 5-HT_3 produces an antinociceptive effect while activation of 5-HT_{1A} receptors has a pronociceptive effect. Activation of 5-HT_2 receptors produces antinociception which may be preceded by pronociceptive responses[29]. Serotonin interacts with other brainstem projection pathways including noradrenaline[28].

Studies were undertaken by Sawynok *et al* (1996), in order to investigate the interactions between serotonergic and noradrenergic systems in the modulation of pain in the rat. They provide evidence that the spinal antinociceptive effects of serotonin are dependent on noradrenaline. This is true as the antinociceptive effect of intrathecal (it) serotonin is reduced by depletion of noradrenaline in the spinal cord after the administration of the neurotoxin 6-hydroxydopamine[30]. The nature of the serotonin-noradrenaline interaction was investigated using pharmacological agents that interact with adrenergic mechanisms in different ways. Serotonin agonists produced a dose-related antinociception. This action was blocked by the administration of a non-selective antagonist for noradrenlaine and an antagonist selective for α_2 receptors but not by the α_1 and α_{2a} antagonist. But this observation is not definitive as α adrenoceptor antagonists could block the action of serotonin and related agonists by a number of mechanisms. Such mechanisms may include serotonin causing the release of endogenous noradrenaline by perhaps a receptor mediated reaction[31]. Serotonin could also interact synergistically with endogenous noradrenaline. The adrenergic system is tonically active within the spinal cord[32] and serotonin may depend on such tonic activity for expression.

In order to determine which serotonin receptors were involved in the interaction a number of serotonin agonists each selective for a different serotonin receptor were administered to rats. Pre-treatment with 6-OHDA produced a marked depletion in noradrenaline levels in the spinal cord (>80%) and reduced antinociception by serotonin and by most of the 5-HT_1 agonists but not the 5-HT_3 or 5-HT_2[28]. The agents that were inhibited by 6-OHDA were potentiated by a systemic pre-treatment of desipramine (blocks the reuptake of noradrenaline). This data presents several possibilities: (1) serotonin releases endogenous noradrenaline from the spinal cord through a receptor mediated action. This indicates that the action of serotonin is augmented by desipramine. This is consistent with a serotonin receptor mediated release of noradrenaline and augmentation resulting from a blockage of the reuptake of noradrenaline. (2) The serotonin receptor involved in this interaction appears to be a 5-HT_1-like receptor[28] as depletion of noradrenaline reduced the antinociception of the 5-HT_1 agonists and not others.

ACTION OF CENTRAL NORADRENALINE AND SEROTONIN RECEPTORS ON GASTROINTESTINAL MOTILITY

Gastrointestinal motility and secretions are modulated by cerebral nuclei via autonomic efferents in a coordinated manner. The sympathetic division of the ANS is important in the control of gastrointestinal function both in the basal and under stressful conditions[33]. Noradrenergic α_2 receptors in the hypothalamus form an important part of this network and research has demonstrated that these receptors have a significant influence on intestinal motility and transit time.

In several species, including humans, the sympathetic nervous system exerts a primarily α_2 mediated tonic inhibitory effect on gastrointestinal motor function[33]. α_1 and β_2 agonists also reduce colonic contractile frequency in non-human primates[34].

Noradrenaline (10 nmol) administered intracisternally (i.c.) significantly decreased gastric motility while yohimbine and not prazosin abolished this decrease pointing towards the involvement of the α_2 receptor in noradrenergic regulation of gastric motility[35]. The α_2 agonist clonidine acting centrally produces a dose dependent decrease in intestinal motility[36]. These studies indicate that central noradrenergic receptors play a role in the modulation of gastrointestinal motility and that alterations in this system may lead to motility symptoms seen in FD patients.

Peripheral serotonin and its receptors effects on gastrointestinal motility have been well established but the control of central serotonergic receptors has been somewhat overshadowed. This may be due to the fact that the majority of serotonin is present in the gut and only 5% exists in the CNS. Some treatment studies suggest that centrally acting serotonergic agents alleviate motility symptoms in FD patients. But it is not clear whether this is due to central or peripheral effects of these drugs. Serotonin is present in enterochromaffin cells (EC) and enteric neurons in the gastrointestinal tract. Release of serotonin from EC cells act as chemical and mechanical transducers for the initiation of local reflexes (peristalsis) and for activation of projections to the CNS[37].

ALTERATIONS IN VISCERAL SENSATION AND POSSIBLE CAUSES

Patients with FD have an increased perception of physiological or minor noxious stimuli in both the fasting and postprandial states[38]. When compared to normal healthy controls, FD patients are hypersensitive to isobaric or isovolumetric balloon distension of the proximal stomach. In view of normal gastric wall compliance in these studies, increased sensation during gastric distension suggests abnormal afferent function or the "irritable stomach syndrome"[39]. This enhanced perception of visceral stimuli may be due to greater sensitivity of visceral afferent pathways or a central amplification of visceral afferent input[40]. Visceral afferent input is modulated by a variety of mechanisms operating between the gastrointestinal tract and the CNS, and dysfunction of these regulatory systems could distort gastrointestinal perception[41]. The ANS which regulates gastrointestinal function is thought to modulate visceral sensitivity. Increased sympathetic tone is known to increase the level of perception of gastrointestinal stimuli without affecting the reflex responses[42]. Alterations in sympathetic modulation of visceral sensitivity may therefore play an important role in FD[41]. Since noradrenaline is the principal neurotransmitter and receptor system involved in the sympathetic nervous system, it may be fair to speculate that there is an abnormality in this system in FD patients. This may be present as an alteration in sensitivity or regulation of the noradrenergic receptor system.

Hypersensitivity of the dorsal horn neurons or altered supraspinal processing of visceral afferent function has been implicated in the increase in visceral sensation[5]. This hypersensitivity may develop in response to descending influences from the brainstem. With regard to the clinical characteristics and the concept of central hypersensivity, a model has been proposed by which abdominal pain in FD could develop by multiple mechanisms either alone or in combination[21]. Stress is involved in the exacerbation of symptoms in FD. Stress induced analgesia is modulated by descending pain inhibitory pathways that are partially mediated by serotonergic systems. This stress induced somatic hypoalgesia can be accompanied by a stress induced visceral hyperalgesia[43]. This may be due to both pain facilitatory and inhibitory systems being activated simultaneously by stress, with the net effect being determined by the contribution of each system[44].

If there is a dysregulation of the descending pain inhibiting serotonergic system, then this would at least partially explain the visceral hyperalgesia of FD patients. Stress is associated with the onset and exacerbation of symptoms in these patients. It may provoke an increase in visceral hyperalgesia in individuals who are vulnerable due to the inability to inhibit the pain facilitatory mechanisms due to a dysregulation of their central serotonergic systems.

ALTERATION IN MOTILITY AND POSSIBLE CAUSES

FD is associated with gastrointestinal motor abnormalities such as delayed emptying[45], impaired initial distribution of a meal within the stomach[46], impaired accommodation[38] antral hypomotility, gastric dysrhythmias (tachygastrias, bradygastrias and mixed dysrhythmias) and altered duodenojejunal motility[5]. The occurrence of dyspeptic symptoms after food digestion suggests a disturbance of postprandial gastric motility which leads to slowed gastric emptying accompanied by sensations of prolonged gastric distension, bloating, and nausea. It was Coffin *et al*[47] that initially suggested that patients with FD may have abnormal motor function of the proximal stomach. Usually, after a meal the proximal stomach relaxes in order to act as a reservoir and to enable an increase in gastric volume without a significant increase in gastric pressure. This impaired accommodation is a disturbance of the "diastolic" function of the stomach and is a frequent finding in FD patients[5].

The underlying mechanism for this impairment of gastric motor is not fully understood. But it has been proposed that there may be a dysfunction of the ANS[48]. Noradrenergic modulation of synaptic vagal transmission in the nucleus tractus solitarus can be assumed to play a role in the modulation of vagovagal reflexes. These include regulation of gastric accommodation, regulation of spontaneous transient lower oesophageal sphincter relaxation and duodenogastric reflexes[40]. Therefore, alterations in this noradrenergic receptor system can lead to abnormalities of motor function and accommodation.

As mentioned, stress plays a role in the onset and exacerbation of symptoms in functional gastrotintestinal disorders such as FD and chronic stress leads to overactivity of these systems. A downregulation of autoreceptors (α_2 and 5-HT_{1A} receptors) was observed in an animal model of social stress[49] and in patients with posttraumatic stress disorder[50] which results in an enhanced release of noradrenaline and serotonin respectively. This enhanced release may lead to a downregulation of postsynaptic receptors (such as β adrenergic and α_1 receptors)[49]. These neuroplastic alterations would initially increase noradrenaline release (presynaptic) but ultimately decrease postsynaptic target neurons. Also excessive release of transmitters could result in depletion of serotonin or noradrenaline further decreasing postsynaptic neuron activation[40].

Stress among other factors can lead to alterations in central aminergic networks involving serotonin and noradrenaline. These alterations may result in changes in the functioning of the ANS and therefore may have an impact on gastrointestinal functions such as motility.

TREATMENT OF FD

Although treatment of FD is expensive, the agents are rarely used in a systematic manner: the majority of treatments are empirical and the results are short lived once the therapy ends. To a degree, this is due to lack of consistent pathophysiologic markers which is why treatment of FD is symptom driven. Eradicating *Helicobacter pylori*, if present, is a first-line strategy. Patients with upper abdominal pain (ulcer-like) as the predominant symptom can initially be treated with proton

pump inhibitors. Those that suffer from dysmotility-like symptoms can be treated with acid suppressive therapy, prokinetic agents or 5-HT_1 agonists. The use of prokinetics is limited due to availability issues[51]. Some studies suggest that 5-HT_1 agonists are effective in the treatment of impaired accommodation[2].

Many patients with FD also suffer from psychiatric disorders including anxiety, mood and somatoform disorders[52] so that the expanding field of psychologic therapies provide a promising area of treatment. Psychoactive agents such as antidepressants and anxiolytics with serotonergic activity have been widely used in the treatment of patients with FD. But it is unclear if these medications improve symptoms through central or peripheral mechanisms[53].

Nonpharmacological interventions have also been employed with two studies having reported a favourable outcome with psychotherapy in FD[53,54]. A Cochrane review on psychological interventions (such as psychotherapy, cognitive behavioural therapy and hypnosis) in FD patients reported beneficial results of such therapy[3].

STUDIES

At present, an integrated disease model that adequately explains the broad variety of symptoms seen in FD, as well as the association with extra-intestinal syndromes and psychiatric disorders is lacking. A number of receptors may be involved in symptom production in FD patients. One study suggests that there is an increased sensitivity of central serotonin receptors in these patients[55]. The authors examined the functional activity of central serotonin by means of a neuroendocrine challenge. The release of the hormone prolactin is partially under serotonin control. The anxiolytic buspirone was used to stimulate the 5-HT_{1A} and increase prolactin release. Although not entirely specific for serotonin receptors (it also acts on dopamine receptors) there is enough evidence to indicate that its mediation of prolactin release is via serotonin receptor as this action can be blocked with the serotonin antagonist methysergide[56]. Dopamine responses in FD were examined using bromocryptine as a probe drug and prolactin decrease as the response. The response of the FD patients was not any different from that of the controls. So it was concluded that buspirone provided an acceptable method of serotonin-stimulated prolactin release. When FD patient were administered the dose of buspirone the response was 200% greater than in healthy controls. This indicates that patients with FD have a supersensitivity of central 5-HT_{1A}[55].

FD is sometimes referred to as upper irritable bowel syndrome (IBS) due to the overlap of symptoms[57]. A down regulation in the noradrenergic α_2 receptors has been implicated in IBS[58]. This may apply to a subgroup of FD patients. The function of these receptors was assessed using a neuroendocrine test. The test was based on the fact that the monoamine reuptake inhibitor desipramine acts on central α_2 receptors to bring about the release of growth hormone[59]. This effect is blocked by the α_1 and α_2 receptor antagonist phentolamine but not by the α_1 antagonist prazosin[60]. IBS patients displayed blunted growth hormone response to a challenge with desipramine at 1 mg/kg body weight. Similar blunted growth hormone responses are seen in depressed patients[61] but this does not account for the blunting here. All patients in this study were assessed by a consultant psychiatrist and while five out of the total 13 were diagnosed with depression both the depressed and the non depressed patients displayed blunted responses[58]. Also it may be argued that delayed gastric emptying and slowed absorption of desipramine might explain the findings. But this was not the case as no further elevations in growth hormone were noted in samples taken later. These results are due to the central action of the α_2 receptors. These findings indicate that the abnormal functioning of these receptors may be important in IBS and a subset of FD and may offer new treatment options[58].

A dose response study using nitroglycerin and clonidine demonstrated that gastric relaxation and antinociception have different effects on the perception of visceral stimuli in humans[38]. Both of these drugs caused relaxation of the fasting stomach without impeding normal postpradial accommodation of the proximal stomach. The gastric balloon distension test was used to measure the antinociceptive effects. Perception scores were reduced with clonidine but not with nitroglycerin. The nitroglycerin actually increased bloating despite significant relaxation. This data suggests that relaxation alone is insufficient to reduce sensation in response to distension in humans[38]. This study suggests that central α_2 receptors are involved in the perception of visceral stimuli and that activation of these receptors produces an analgesic effect in FD patients. This suggests that these patients may have some abnormality of the α_2 receptors that may influence the hypersensitivity seen in FD patients.

In summary the main symptoms of FD are alterations in motor function and abdominal pain. The mechanisms involved in the modulation of these functions include central serotonergic and noradrenergic receptor systems. Both human and animal studies indicate that there are abnormalities in these systems in FD which may account for the symptoms of FD.

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