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TOPIC HIGHLIGHT

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Cholecystokinin hyperresponsiveness in functional dyspepsia

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Abstract

Functional dyspepsia (FD) is a common disorder of yet uncertain etiology. Dyspeptic symptoms are usually meal related and suggest an association to gastrointestinal (GI) sensorimotor dysfunction. Cholecystokinin (CCK) is an established brain-gut peptide that plays an important regulatory role in gastrointestinal function. It inhibits gastric motility and emptying via a capsaicin sensitive vagal pathway. The effects on emptying are via its action on the proximal stomach and pylorus. CCK is also involved in the regulation of food intake. It is released in the gut in response to a meal and acts via vagal afferents to induce satiety. Furthermore CCK has also been shown to be involved in the pathogenesis of panic disorder, anxiety and pain. Other neurotransmitters such as serotonin and noradrenaline may be implicated with CCK in the coordination of GI activity. In addition, intravenous administration of CCK has been observed to reproduce the symptoms in FD and this effect can be blocked both by atropine and loxiglumide (CCK-A antagonist). It is possible that an altered response to CCK may be responsible for the commonly observed gastric sensorimotor dysfunction, which may then be associated with the genesis of dyspeptic symptoms.

Key words: Functional dyspepsia; Cholecystokinin hyperresponsivenes; Stress; Sensorimotor dysfunction

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INTRODUCTION

Functional dyspepsia (FD) is a heterogeneous condition of uncertain etiology. It is a common disorder frequently encountered, both in the primary care and specialist clinics. FD in the current Rome II criteria refers to, persistent upper abdominal pain or discomfort with or without symptoms of fullness, bloating, early satiety and nausea, with no identifiable organic cause. Excluded are patients with reflux symptoms and lower gastrointestinal (GI) symptoms. It also stipulates that symptoms must be present for at least 12 wk which need not be consecutive, in the preceding 12 mo[1]. The symptoms patients complain of are variable, occasionally very disabling and associated with a reduced quality of life, which is determined by symptom severity. The dyspeptic symptoms are usually meal related, however the temporal relationship between dyspeptic symptoms and meal intake need to be studied further. Symptoms are usually intermittent and can be aggravated by food[2] and stress[3]. Depending on the symptom clusters, patients may be categorized into different subgroups. Dysmotility-like dyspepsia describes a group that, on symptoms alone, appears to have GI sensorimotor dysfunction. The other two subgroups include Ulcer-like dyspepsia and mixed group. Studies have implicated among others GI dysmotility, gastric hypersensitivity, abnormality of accommodation and an altered brain-gut communication as important pathophysiological correlates of FD. It can be thought of as a biopsychosocial disorder, in that there is an underlying GI sensorimotor dysfunction with an important input from the psyche[4].

Cholecystokinin (CCK) is an established brain-gut peptide that plays an important regulatory role in gastrointestinal function. CCK is involved in the control of food intake in both man and animals[5-7]. It inhibits gastric motility and emptying via capsaicin-sensitive vagal pathways in rats[8]. In human studies, CCK mediates gastric emptying under physiological conditions[9]. It also inhibits food intake and increase satiety in humans[10]. CCK appears to be involved in the gastric response to the presence of several intestinal stimuli, including fat and protein. In humans, CCK pathways modulate sensations induced by gastric distension[11]. It has also been hypothesized that CCK plays an etiologic factor in panic disorder and anxiety[12], factors that may be important in precipitating or aggravating symptoms in FD patients. CCK plays an important role in the brain-gut axis, allowing peripheral signals from the gut to modulate central pathways and vice-versa. An altered CCK function in terms of response to food intake, abnormal central response to stressors or

even disturbed effect on gut sensorimotor functions may be responsible for the dyspeptic symptoms in FD and involved in the pathophysiology of this common disorder.

SYMPTOMATOLOGY IN FD

The correlation between symptoms and proposed impaired GI function is still unclear. Stanghellini investigated the relationship between symptom severity, demographic features and gastric dysmotility in a large series of FD patients[13]. They were able to identify two main subgroups, the first has predominant epigastric pain, male gender and normal gastric emptying, while the second group is characterized by predominantly nonpainful symptoms, female gender, a high association with irritable bowel syndrome (IBS) and delayed gastric emptying. The same group also reported that postprandial fullness and severe vomiting were independently associated with delayed gastric emptying of solids. These findings were confirmed by Sarnelli *et al* who studied the relationship between FD and delayed gastric emptying of solids or liquids and discovered that delayed gastric emptying of solids was constantly associated with postprandial fullness and vomiting. While delayed emptying of liquids was associated with early satiety and postprandial fullness[14]. However the above findings were disputed by Talley *et al* who found no predictive value using specific symptoms to identify alterations of gastric emptying[15].

Studies have suggested that in FD, gastric accommodation is normal during fasting but is impaired after a meal, due to failure of proximal stomach relaxation[16,17]. Other reports suggested that impaired accommodation is associated with symptoms of early satiety and weight loss. Furthermore restoring gastric accommodation with fundus relaxing drugs, 5HT1 agonists sumatriptan and buspirone[18], Tack *et al* were able to improve the symptom of early satiety. The above findings however, were contradicted by Boeckxstaens *et al* who could demonstrate no difference between postprandial symptoms and proximal stomach function[19]. Hypersensitivity to gastric distension has previously been reported in FD[20], but it is present only in a subset of patients. The relevance of this particular characteristic observation was studied by a group from Belgium[21] who discovered that gastric hypersensitivity is associated with symptoms of postprandial epigastric pain, belching and weight loss. Similar observations were reported by Salet *et al* who reported that gastric visceral hypersensitivity plays an important role in the pathogenesis of upper gastrointestinal symptoms especially nausea, abdominal bloating and pain[22].

More importantly FD patients were known to report symptoms after a meal, including fullness, bloating, epigastric pain, nausea and vomiting. Based on symptoms alone, this seems to suggest an underlying gastric sensorimotor disorder. However the temporal relationship between symptoms, meal ingestion and gastric dysmotility has not been truly examined. Ingestion of a fatty meal in FD patients will result in the induction of dyspeptic symptoms[2]. The presence of nutrients in the small intestine slows gastric emptying and suppresses appetite and food intake which is mediated in part by CCK[23,24]. CCK has also been implicated in the induction of nausea in healthy subjects[25,26]. It relaxes the proximal stomach[27] and delays gastric emptying. Thus CCK may play an important role in symptoms production in patients with FD.

CCK AND GI HYPERSENSITIVITY

Prevalence of hypersensitivity to gastric distension in FD has previously been reported[20,28,29]. Gastric distension is perceived as painful at smaller distending volumes and lower pressures compared to a group of healthy controls. The observed hypersensitivity to gastric distension is associated with epigastric pain, belching and weight loss. There is also evidence of sensitivity to other stimuli including acid and digestive products of fat and protein. Furthermore we have previously demonstrated that FD patients responded differently to an infusion of CCK octapeptide (CCK-8), compared to a group of healthy and disease controls[46].

Response to CCK-8 was assessed by an intravenous CCK-8 infusion (6 ng/kg per minute) in a double-blind, cross-over fashion using normal saline solution as placebo infusion. The test was deemed positive when the infusion reproduced part or all of the patients' symptoms. The severity of the response was evaluated on a simplified visual analog scale (VAS). The VAS allowed us a reproducible method of assessing symptoms and a crude form of grading patients' responses. It also provided a means of analyzing severity of symptoms and allows us to grade individual's responses to the CCK-8 infusion. Furthermore we can also determine the efficacy of atropine and loxiglumide in alleviating symptoms.

The most common reproducible symptom in the CCK challenge test is that of upper abdominal pain. This is usually associated with a feeling of abdominal bloating and satiety. Other symptoms included borborygmia, nausea, vomiting, light-headedness and occasional heartburn. The test is negative if the infusion fails to precipitate any symptoms or only an occasional mild discomfort. In some cases the precipitated symptoms were so severe that the infusion had to be discontinued due to patients' distress. Majority of FD patients had a positive response to the CCK-8 challenge. In all the responders, the symptoms produced were quite marked and there was little doubt about the diagnosis. None of the healthy controls reported any significant symptoms to the CCK-8 infusion. The few that experienced minor epigastric discomfort or nausea can be explained by the physiological action of CCK. None of the subjects reported any sensation from the saline infusion.

It was also demonstrated that the response to CCK-8 can be blocked by atropine in a dose dependent fashion. Atropine also managed to prevent recurrence of symptoms to further CCK-8 infusion. The CCK-8 challenge test, likewise can be attenuated using the CCK-A antagonist loxiglumide.

Scintigraphic gastric emptying was also determined in the FD group of patients using radiolabelled technetium and solid phase gastric emptying was shown to be significantly delayed in this group of patients compared to

a group of healthy controls.

Katchinski demonstrated that sham feeding in healthy volunteers brought about a stimulation of gastrointestinal motility implying a cephalic stimulation of GI motility. He also showed that the peripheral acting cholinergic antagonist atropine completely abolished antral activity and consequently coordinated antroduodenal motor activity, while Loxiglumide inhibits cephalic stimulation of antral contractions[30]. Furthermore, atropine completely blocked the changes in gastric function induced by stimulation of the nucleus raphe obscurus[31]. Similarly, the dyspeptic symptoms produced by the CCK infusion were completely abolish by atropine, indicating the importance of the vagal efferent pathways in mediating this response. The suppression of response by atropine may occur also at the level of the peripheral muscarinic receptors, at the junction of the gastric musculature or the secretory glands.

Hypersensitivity to CCK may explain the abnormal response to CCK infusion in dysmotility-type FD patients. The exaggerated response to CCK in this group of patients may be the basis of the pathophysiology of the condition and also account for the observed dyspeptic symptoms. Exogenous CCK may act on primary afferent neurons that are also gastric mechanoreceptors and there follows activation of a vago-vagal reflex pathway, which leads to relaxation of the body of the stomach[8,32-34]. Early satiety and post-prandial fullness may be mediated via the afferent sensory pathways or through central CCK interconnections. Meanwhile, abdominal discomfort, pain, distension, nausea and vomiting may result from excessive fundal relaxation mediated via the motor limb of the vago-vagal reflex, activated by CCK, gastric distension or possibly a combination of both. This reflex results in the inhibition of gastric emptying which is a predominant feature of FD. Any abnormalities which up-regulate sensory signals anywhere within the central nervous system and enteral nervous system (CNS-ENS), could induce hypersensitivity leading to pain and discomfort which characterise FD. Over stimulation of the afferent limb of the multiple sensorimotor reflexes anywhere from the GI tract to the CNS could trigger a motor response. Depending on the pathway stimulated, a different response will be obtained.

CCK CHALLENGE TEST AS A DIAGNOSTIC TEST

FD is a diagnosis of exclusion, though a positive diagnosis can be made based on the symptoms[1], efforts should be made to exclude organic diseases if there were presence of "alarm signs or symptoms". The CCK-8 challenge test may be used as a diagnostic tool to positively identify dysmotility type FD. For it to be effective the challenge test should be safe, able to reproduce patients symptoms, response should be reproducible and dose dependent and blocked by the antagonist and most importantly specific to the disorder. We have shown that the test is safe and can precipitate the patients' symptoms which can be blocked by Atropine and Loxiglumide (CCK antagonist). The CCK-8 challenge test is dose dependent, in that no response was seen with 2 ng/kg per minute, moderate response seen with 4 ng/kg per minute and best response identified with the 6 ng/kg per minute. The test is reproducible in that in 10 patients when the test was repeated on a separate day, there was no significant difference in the reported symptom severity (on the VAS), score of 35 (5) *vs* 36 (7) [mean (SD)]. However the test needs to be tested further in other functional disorders especially in Irritable Bowel Syndrome (IBS) patients or patients with Non-erosive reflux disease. Thus more work need to be done before the CCK-8 challenge test can be reliably used as a diagnostic test.

FOOD SENSITIVITY AND CCK IN FD

CCK is released by the duodenum in the presence of digestive products of fats and proteins in the intestine[35]. We have previously seen that physiological CCK relaxes the stomach, constricts the pylorus[36,37] and inhibits gastric emptying,[38] and thereby increases gastric distension. This effect of CCK is mediated via gastric vagal afferents[10]. Furthermore in healthy subjects, the combination of duodenal lipid and gastric distension induces meal-like fullness and nausea. Duodenal lipid reduces gastric tonic and phasic activity during distension, and this can be partially block by loxiglumide[39]. This signifies that CCK-A receptors are implicated in the cause of nausea and postprandial fullness, associated with duodenal lipid infusion. The increased gastric distension induced by the delayed gastric emptying may be the method by which CCK reduces food intake[5,38].

Similarly in FD the presence of certain nutrients especially fat, in the intestine can generate dyspeptic symptoms, including nausea, bloating, pain and fullness[40-43]. Feinle *et al* demonstrated that in the FD patients, duodenal infusion of lipid aggravates the hypersensitivity to gastric distension. This effect is specific for fat, and evidence suggests the participation of CCK[44]. The fat induced dyspeptic symptoms can also be abolished by dexloxiglumide (CCK-A antagonist) signifying an involvement of CCK-A receptors[42]. The underlying mechanism is probably due to hypersensitivity to CCK. We postulate that it is CCK that enhances the distension effect, rather than distension enhancing the effects of CCK. Furthermore recordings from the afferent vagal nerve indicates that mechanoreceptors sensitive to gastric stretch respond more strongly in the presence of CCK[45].

Endogenous CCK released in response to lipid infusion acts in a paracrine fashion to stimulate CCK-A receptors. The information is then transmitted to the CNS via vagal afferent nerves. This pathway is involved in the feedback inhibition of gastric tone and motility which could indirectly gives rise to the observed symptoms[42,46]. However CCK may not be the only factor involved in the above vagal reflex pathway. It is more common indigestion, trying to eat when we are emotionally stressed[5]. Psychological and physical stress has been shown to cause slowing of gastric emptying in animals. Furthermore, excitation of the sympathetic nervous system by stressors increases visceral sensitivity[47,48].

ROLE OF CENTRAL SEROTONERGIC AND NORADRENERGIC RECEPTORS

Stress also plays an important role in precipitating or aggravating symptoms in FD. Central serotoninergic (5HT) receptors are important in mediating the stress response. Utilizing the Buspirone Neuroendocrine challenge test, we have previously shown that FD patients have hypersensitive central 5HT receptors functioning[49]. The release of prolactin from the anterior pituitary is under the inhibitory control of dopamine and stimulatory control of 5HT. Buspirone, an azaspirodecanedione, stimulates central 5HT1A receptors and causes prolactin release in a dose dependent manner, and the extent of prolactin release post stimulation can be used as an index of central 5HT receptors function. Prolactin release following Buspirone challenge was reported to be significantly greater in FD patients. 5HT plays an important role in the control of GI function both peripherally at the ENS and also centrally at the CNS. Similarly, we have also shown that the observed hypersensitivity of the central 5HT receptors were highly correlated with delayed gastric emptying[50].

Central noradrenergic pathways are also important in the mediation of the stress response. α-2 receptor activation mediates inhibition of a number of gastrointestinal functions including intestinal motility. Its activation also inhibits acetylcholine release from the vagal nerve. Previously we have shown that the central α-2 receptors are hyposensitive in patients with delayed gastric emptying[51] using the desipramine neuroendocrine challenge test. In this test, subjects were challenge with desipramine, a monoamine reuptake inhibitor, which blocks the reuptake of noradrenaline when given orally. This indirectly stimulates growth hormone release by acting on central α-2 receptors situated in the hypothalamus.

In fact FD patients who have an abnormal response to the CCK-8 challenge test, have been shown to have hypersensitive central 5HT receptors (as evidenced by an exaggerated prolactin response to buspirone challenge) and hyposensitive central α-2 or noradrenergic receptors (as evidenced by a blunted growth hormone response to Desipramine challenge). Gastric emptying was also shown to be delayed in this group of patients[52]. Kendrick established that injections of CCK stimulated significant increase of noradrenaline and serotonin in the paraventricular and supraoptic nucleus. Both hypothalamic nuclei receive noradrenergic and serotonergic inputs and are important in the regulation of feeding and control of GI motility. The principal action of systemically administered CCK centrally is via the nucleus tractus solitarius (NTS) which projects directly or indirectly to the paraventricular nucleus (PVN) and supraoptic nucleus (SON) and the dorsal motor nucleus of the vagus (DMV). In the PVN, systemic injections of CCK activate neurons which influence feeding behaviour and affect gastric motility[7,33].

CCK AND PSYCHOLOGICAL STRESS

Both depression and chronic tension can present with abdominal symptoms[53,54]. Studies have shown that patients with FD have increased levels of anxiety. Gomez and Daly reported that 22% of their FD patients had chronic tension and a further 15% demonstrated hysterical symptoms[55]. Mangi *et al* reported that two thirds of 30 consecutive outpatients with FD met DSM-III criteria for anxiety disorders[56]. The neurotransmitter CCK can be found in abundance in the brain. Two receptor subtypes (A and B) have been identified within the CNS. CCK-B receptors are more numerous and widely distributed in the CNS[57-59]. CCK or CCK receptors are discovered in areas of the brain involved with cognitive or emotional aspects of behaviour[58,60]. It is known to interacts with other neurotransmitters in the CNS (monoaminergic, serotonergic, GABAergic) known to be involved in anxiety and affective disorders[61-63]. Chronic treatment with imipramine, which inhibits noradrenaline and 5HT reuptake, could antagonize the panic causing effects of CCK-4 in panic disorder patients, indicating that these monoamines may be important in interacting with CCK in promoting panic symptoms. Thus CCK-B receptor plays an important role in anxiety states and panic attacks[12,64,65]. CCK-B receptors can modulate activity within the hypothalamic-pituitary-adrenal (HPA) axis[65,66], which is involved in the stress response.

Psychological stress is widely believed to precipitate exacerbation of symptoms in FD. Inhibition of gastric emptying and stimulation of colonic transit is the most consistent motility response of the GI tract to acute stress. An organism's response to stress is generated by a complex integration of neurons in the CNS. Main output of this integrated central network to the periphery (which is activated in response to various stressors, both physical and psychosocial) includes autonomic and neuroendocrine responses together with modulation of pain. Present evidence strongly suggests that acute stress affects visceral sensitivity in humans. Whether chronic stress plays the same role remain to be seen. Early life stress and trauma, in the form of abuse, neglect, or loss, play a major role in the vulnerability of individuals to develop functional GI disorders. It is proposed that in the genetically predisposed individual, both early life stress and severe life-threatening stress can result in permanent alteration in central stress circuitry and predisposes the individual to the development of functional disorders later in life.

LOXIGLUMIDE IN THE TREATMENT OF FD

If CCK plays an important role in the pathophyphysiology of FD then the use of Loxiglumide (CCK-A receptor antagonist) should be effective in the control of the symptoms. A randomized, double-blind, parallel group, placebo-controlled trial was conducted in 28 symptomatic FD patients (8 male, 20 female, aged 19-59 years, mean age 33). All patients satisfy the Rome II criteria for the diagnosis of FD. They all have normal endoscopy, normal abdominal ultrasonography, a positive CCK provocation test (symptom appearance after CCK-8 6 ng/kg iv infusion) and delayed (half emptying time > 60 min for the solid phase) gastric emptying of a radiolabeled, mixed solid-liquid meal of about 400 Kcal. Patients were randomly assigned to placebo or

Loxiglumide 400 mg three times daily for 8 wk. Response to treatment was evaluated on a Visual Analogue Scale to generate a Cumulative Symptom Score (CSS). Despite an expected high rate of placebo response, a quicker, more pronounced, and sustained symptomatic relief was observed during treatment with loxiglumide. There were 11 of 12 responders on Loxiglumide compared to only 6 of 11 on placebo ($P = 0.04$ Chi-square test). Loxiglumide also showed an acceleration of solid phase gastric emptying whereas placebo did not show any effect. However there was no correlation observed between increased gastric emptying and clinical improvement. Thus Loxiglumide is effective in the treatment of symptoms of FD and has a prokinetic effect. However, we need further studies on a larger population of patients to confirm the findings[67].

In summary, the discomfort, pain and altered sensations (to intraluminal stress) that characterize FD are considered to represent visceral hyperalgesia. Mechanisms by which functionally disordered visceral receptors, respond abnormally to normal everyday stimuli remain unknown. However, it is also possible that an aberrant input to the CNS or altered CNS pathways (5HT, Noradrenergic and central CCK) could contribute to the observed visceral hyperalgesia and dysmotility. Hypersensitive visceral CCK receptors may be modulated by central pathways primed by stress or trauma. The receptors will then respond inappropriately to normal stimuli, activating efferent pathways via a vago-vagal reflex pathway to cause perturbation of peripheral sensorimotor functions. This may be the basis for the genesis of the symptoms encountered in FD.

Furthermore, the CCK-8 challenge test may also be a useful tool for the diagnosis of Dysmotility type FD, but this will need further evaluation.

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