Neuropeptides and Anxiety: Focus on Cholecystokinin  
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Cholecystokinin (CCK), a gastrin-like neuropeptide, exists in the central nervous system in several forms. The octapeptide (CCK-8) occurs in predominantly sulfated form (CCK-8S), and the tetrapeptide (CCK-4) occurs in smaller but significant quantities. This review highlights recent developments in preclinical and clinical research into the potential role for CCK in mediating anxiety states. Relevant animal and human studies of administration of CCK agonists are described, as well as recent data regarding the concentration of CCK-8S in cerebrospinal fluid from patients with panic disorder, bulimia nervosa, and obsessive compulsive disorder. Finally, the development of agents that specifically antagonize CCK receptors will be described, as will potential therapeutic uses for these new compounds.

Indexing Terms: mood disorders/bulimia nervosa/neurotransmitters/panic disorder/cerebrospinal fluid

Increasing preclinical and clinical evidence implicates cholecystokinin (CCK), a gastrin-like material found in the mammalian intestinal tract and central nervous system (CNS), as a modulator of neuronal functioning.1 CCK was first reported to occur in mammalian brain in 1975 (1). CCK occurs in the CNS predominantly in two forms: CCK tetrapeptide (CCK-4) and CCK octapeptide (CCK-8). These neuropeptides appear to act as neurotransmitters themselves and to modulate the activities of several other neurotransmitters and various neuropeptides. The predominant form of CCK in the CNS is the sulfated form of the octapeptide (CCK-8S), while CCK-4 exists in smaller concentrations. There are two predominant receptor subtypes for CCK: the CCK-A receptor (for "alimentary")2 and the CCK-B receptor (for "brain") (2). CCK-A receptors have a high affinity for CCK-8S and lesser affinity for desulfated CCK-8, CCK-4, and gastrin. The CCK-A receptors predominate in the periphery, and occur in high concentrations in the viscera as well as in the CNS (3). The CCK-B receptors, which have a high affinity for all CCK agonists, are the predominant form in the brain. The type A receptor in the CNS mediates satiety and other functions, while the B receptor appears to be important in mediating anxiety.

The first description of the anxiogenic effects of CCK were reported in a study of the mechanism for satiety in sheep (4). In this study, pentagastrin was infused into the lateral ventricles of sheep and unexpectedly elicited behaviors consistent with anxiety, such as foot stamping and vocalization. Subsequent studies in vitro and in vivo have supported the hypothesis that CCK is an important neuropeptide in the mediation of anxiety in animals and in humans. This review will survey relevant preclinical and clinical studies supporting a role for CCK in anxiety, and will also review the development of a new class of CCK-antagonist compounds with potential clinical utility.

Preclinical Studies

Early work by Bradwejn and de Montigny (5, 6) showed that benzodiazepines specifically antagonized CCK-8S-induced excitation of rat hippocampal pyramidal neurons but did not block the actions of other neurotransmitters such as acetylcholine, aspartate, or glutamate. Additionally, they showed that the antagonism of the CCK-8S-induced excitation was specific for benzodiazepines, as demonstrated by a lack of effect of haloperidol, phenobarbital, and meprobamate on this paradigm (6). These were the first experiments showing antagonism of a central action of a neuropeptide by a benzodiazepine. Behavioral experiments also supported a role for CCK in mediating anxiety. Injection of CCK-8 into the amygdala enhanced behavioral arousal and fear-related motivation behaviors in rats at very low doses (7). A substantial literature on the anxiogenic potential of CCK agonists has emerged over the past several years, and supports the role of the CCK-B receptor in mediating these effects (8). Recently, CCK agonists have been studied in nonhuman primates. Ervin et al. described the effects of intravenous administration of CCK-4 to African green monkeys (9). The behaviors elicited were consistent with fear/panic-like responses, including vigilance, agitation, restlessness, and, at peak levels of intensity of the reactions, immobility or freezing, which could be analogous to the human equivalent of panic. The response of the individual monkeys was related to social hierarchy and to baseline behavioral characteristics of the individual animals. Pretreatment with alprazolam or a specific CCK-B receptor antagonist attenuated the effects of the CCK-4 challenge (10).

Additional support for a potential role for CCK in mediation of anxiety states is the demonstrated interaction of this peptide with neurotransmitters implicated in anxiety states, such as y-aminobutyric acid (GABA), serotonin, and norepinephrine. Interaction with the GABA receptor complex, initially demonstrated in the experiments described above in which benzodiazepines effectively and selectively blocked CCK-8S-induced hippocampal neuronal excitation (5, 6), is further supported by the observation that CCK and GABA are colocalized in CNS neurons in cortex, hippocampus, and
amygdala (8, 11). Further, there appears to be a functional interaction between benzodiazepine treatment and the density of CCK receptors in certain brain areas; this interaction may have potential links to tolerance withdrawal and to the anxiolytic effects of the benzodiazepines (12). Serotonin (5-HT), which has been implicated in anxiety, interacts with CCK. Administration of ondansetron, a specific 5-HT3-receptor antagonist with anxiolytic properties, inhibits the release of CCK-like immunoreactivity from limbic areas in rodents (13). Evidence indicating an interaction between norepinephrine and CCK includes the upregulation of CCK receptors in hippocampus and frontal cortex after chemical lesion of the locus ceruleus, a midbrain noradrenergic nucleus believed to mediate fear and arousal states (14).

Clinical Studies: Role of CCK in Stress and Panic Anxiety

CCK appears to play a role in stress responses in humans. In one recent study of marathon runners (15), 19 athletes (8 women, 11 men) who were about to participate in a 46.5-km run were assessed for stress-related compounds (cortisol, corticotropin, CCK, norepinephrine, and gastrin) before and after the race, as well as during a control condition. As expected, most of the stress-related compounds were increased before the race, with CCK being the most increased. The authors hypothesized that CCK was related to anticipatory anxiety in these individuals (15).

CCK-4 has been studied as a panic-inducing agent in humans. To expand on the preclinical data as well as the clinical observation that CCK-4 can induce panic-like symptoms in healthy volunteers (16), Bradwejn et al. embarked on a series of experiments to characterize the panicogenic effects of CCK-4 in humans (17). Initial studies indicated that patients with panic disorder experienced panic attacks after intravenous administration of 50 μg of CCK-4 but not after receiving a placebo (18). Subsequent studies indicated enhanced sensitivity to CCK-4 in panic disorder patients vs normal volunteers (19). The symptom profile—e.g., palpitations, shortness of breath, dizziness, dyspnea, and cognitive symptoms such as fear of losing control of one’s mind or body or of dying—elicited by CCK-4 in panic disorder patients appears to be similar to the effects of carbon dioxide, another panicogenic agent; both agents elicit panic attacks that are described by patients with panic disorder as being symptomatically similar to those experienced unexpectedly (20). Bradwejn et al. also demonstrated that the CCK-4-induced attacks could be effectively prevented by pretreatment with a CCK-B antagonist (21). Interestingly, another CCK-like peptide, pentagastrin, which differs by only one amino acid from CCK-4, appears to be panicogenic in individuals with panic disorder (22) and elicits symptoms similar to those elicited by CCK-4 (23).

Although enhanced sensitivity to CCK-4 in panic disorder patients has been demonstrated, the mechanism by which the CCK-4 exerts its panicogenic effects remains incompletely understood, there being no direct evidence that CCK-4 crosses the blood–brain barrier after intrave-}

nous administration. It has been hypothesized that the effects of this peptide may be exerted on areas of the brain where the blood–brain barrier is incomplete, such as the nucleus tractus solitarius (NTS) (9). This nucleus plays an important role in mediating afferent input from periphery and in acting as a relay for efferent signals that control vegetative functions, and may mediate autonomic discharge such as occurs during unexpected (and possibly CCK-induced) panic attacks (24). For example, most NTS neurons exhibit prolonged excitation after administration of CCK-B agonists, whereas CCK-A agonists, which presumably interact with CCK-A receptors present in the NTS, exert inhibitory effects on NTS neurons and also elicit brief, but not prolonged, excitation (8, 25). These observations suggest that the NTS may potentially mediate at least in part some of the panicogenic effects of CCK-B agonists in humans.

Human Cerebrospinal Fluid (CSF) Studies of CCK

On the basis of the accumulating evidence of abnormal CCK function in panic disorder, my colleagues and I examined CSF concentrations of CCK-8S in panic disorder patients and in normal comparison subjects (26). We measured CCK-8S because methods for measuring CCK-4 in CSF are not sensitive enough, but the octapeptide is present in quantities sufficiently large (i.e., ng/L) to be measured. As can be seen in Fig. 1, CSF concentrations of CCK-8S in panic disorder patients were lower than in normal comparison subjects. The finding of lower CSF concentrations of CCK-8S in panic disorder was thought to possibly reflect a reciprocal relationship between CCK-8 and CCK-4 in the CNS (27), and might be a reflection of increased CCK-4 activity, with a resulting reciprocal decrease in CCK-8 activity.
Alternatively, there may be increased receptor sensitivity or lower CCK-8 production, as reflected by the lower CCK-8S concentrations in CSF in the panic patients. We also measured CSF concentrations of CCK-8S in a small number of patients with obsessive compulsive disorder, another clinically significant anxiety disorder (28). In this small number (n = 11) of patients, CSF concentrations of CCK-8S were not different from those in the normal comparison subjects, suggesting that alterations in CCK function, as reflected by CCK-8S concentrations, may not be present in all anxiety disorders.

We subsequently measured CCK-8S concentrations in patients with bulimia nervosa, a condition characterized by uncontrolled eating binges and purging behaviors (Fig. 2). The CCK-8S concentrations in CSF in patients with bulimia nervosa were also lower than those of the normal comparison subjects (29). Because bulimia nervosa could be characterized, in part, as one of dysregulated satiety, the finding seemed to be consistent with the theory that the central CCK function in bulimia nervosa was abnormal, paralleling studies indicating that the peripheral CCK-8 function was abnormal (30). Interestingly, the CCK-8 concentrations in the subjects in this CSF study did not correlate with any of the core symptoms of the eating disorder (e.g., binge frequency or intensity, purging), but did correlate with measures of anxiety, interpersonal sensitivity, and anger/hostility. This raised the possibility that the CSF abnormalities of CCK-8S observed in bulimics might be associated more with abnormal levels of anxiety than with core symptoms of eating disorder in this patient sample.

CCK Receptor Antagonists

In recent years, specific and highly potent antagonists for CCK receptors have been discovered and developed (31). One of the first antagonists discovered was asperlicin, a naturally occurring benzodiazepine derived from a fungus. Subsequently, both benzodiazepine and non-ben-
zodiazepine-like agents have been developed that are selective for either the CCK-A or CCK-B receptor (Fig. 3). As a group, these compounds may represent a novel pharmacological group. In rodents, CCK-B antagonists appear to be potent anxiolytics (32); human studies are planned. These agents also appear to have the ability for blocking withdrawal from benzodiazepines (33) or alcohol (34). The CCK-B antagonists appear to be relatively nonseeding, and apparently do not produce dependence or withdrawal after chronic administration (32). Thus, they may represent an alternative treatment for both alcohol and benzodiazepine dependence, if future research confirms the promising early data in this area. Additionally, because long-term treatment is required for many of the anxiety disorders, these agents may have some advantages over the existing long-term treatments for anxiety disorders, although considerable research is required to ascertain this.

In summary, the effects of the CNS cholecystokinin system in mediating anxiety appear to be expressed predominantly through the CCK-B receptors. The availability of selective antagonists for CCK receptors has allowed for initial studies to test appropriate hypotheses generated from the preclinical and clinical studies to date. New therapeutic agents may evolve from this line of research, which could significantly improve our ability to treat various psychiatric and substance abuse disorders. The next decade should provide interesting and clinically relevant information regarding the role of CCK and CCK antagonists in anxiety and in the treatment of anxiety disorders.

References