

EDITORIAL

Secretin's role in the cerebellum: A larger biological context and implications for developmental disorders

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Evolutionarily conserved primitive learning and memory networks including the cerebellum employ classical neurotransmitters and peptides sustaining their actions (1). Children learn to perform communicative, affiliative adaptive acts that promote an overall state of well-being and maintain homeostasis. The cerebellum is critical to learning and memory of these adaptive acts. Yung and colleagues' review (this issue) of the role of secretin in the cerebellum draws upon innovative studies conducted in both basic and clinical settings. Their main conclusions are supportable and help advance translational research on secretin and developmental disorders. The authors describe secretin as a retrograde messenger and neuromodulator within the cerebellum and discuss its candidacy as a molecule in the treatment of autism and related spectrum disorders. The contention that secretin's role in developmental disorders should not be dismissed on the basis of studies published to date is a critical point that is supported by the experiments of Yung and colleagues, by work in our laboratory (2–4) and by a careful reading of the literature. We would like to expand upon the ideas presented in their article.

Secretin's role in regulation of stress

Yung and colleagues' review is especially intriguing if placed in the context of the overall role that neuropeptides such as secretin play in the modulation of stress across systems and their concomitant effects on development and behavior. It is thought that secretin is expressed at a relatively low level in the CNS. Indeed our own studies show that secretin's constitutive expression in the fore-brain is undetectable in a freely moving rat but robustly

up-regulated in response to an oxidative stressor, colchicine. Based on this finding, and in light of reports by Yung and others, we hypothesize that secretin is a centrally acting stress-regulatory neuropeptide synthesized and released in the brain, as it is in the gut, in response to homeostatic challenges (3). From this perspective, the actions and regulation of secretin in the cerebellum may well prove to be part of a unified and integrated stress-modulatory neuropeptide mechanism distributed throughout the CNS and periphery (4).

The findings of Yung et al. on the cerebellum support the importance of secretin's role in learning and memory networks and the conditioning of adaptive behaviors. The midline cerebellum is part of an integrated network that regulates emotional states and behavioral expressions involving interconnections of the cerebral and cerebellar cortices and their subcortical outlets including the amygdala, hypothalamus and periaqueductal gray (5). Learning and memory of fear responses, as reflected in changes of somatic and autonomic response patterns such as freezing, are altered by manipulating the cerebellar vermis (6). These response patterns are critical to conditioning of cognition, emotional control, and execution of adaptive actions. Cerebral cortical thalamostriatal stress adaptation networks processing information from the midline cerebellum are dysregulated in disorders of development, including autism.

The cerebellum is part of an integrated network regulating emotional behaviors that appears to be abnormal in autistic patients. Childhood cognitive and emotional disorders associated with cerebellar damage include language difficulties, disinhibition, impulsivity and irritability, and failure to initiate and execute actions (7). Autistic patients exhibit

cerebellar syndromes, akin to symptoms seen in experimental animals and patients with localized cerebellar damage (8). Fear conditioning results in synaptic changes in the cerebellum, amygdala, and hippocampus, all three brain regions thought to be abnormal in autism and in other patients exhibiting symptoms of cerebellar syndromes (6). Reduced numbers and volume of Purkinje cells have been reported in the cerebellum of autistic patients (9,10). Both Pavlovian eye-blink conditioning and Pavlovian fear conditioning are dependent on the functional integrity of two structures, the amygdala and the cerebellum. Yung reviews the finding that Purkinje neurons are responsible for the classical conditioned eye-blink response and that similar functions may be modulated or controlled by secretinergic systems. The hypothetical consequences of impairments in secretin's regulation, synthesis, or modulation of other systems in the CNS might be detected as impairments in cerebellar function.

Secretin's connection to the viscera

The autistic brain demonstrates sites of pathology of brain structures that react to visceral inflammation by generating defense reactions involving cross-talk between the cerebral and cerebellar cortices and visceral organs (8). Both the brain and the viscera are endowed with the distributed property of memory employing many of the same neurotransmitters and peptides including members of the secretin peptide family.

Visceral state-related information processed by the midline cerebellum transmits via the principal vagal relay nuclei of solitary tract and pontine parabrachial complex to vermal/fastigial zones and thalamocortical striatal networks involved in perceptions and the drives motivating goal-directed adaptive behaviors. The medial vermal cortex of lobule VII receives vagal afferent signals via climbing fibers (11). The vagus nerve, particularly its afferent pathway, plays an essential role in the physiological actions of secretin (12). The finding in two autistic children of 50% fewer secretin cells in the duodenum (Gershon MD and D'Autreaux. Personal communication. 2003) suggests that impaired secretin systems would impair vagal transmission. Vagal stimulators that ameliorate depression and intractable epilepsy (13,14), may act in part by reflexively stimulating release of secretin from the brain-gut stress regulatory axis. Autistic children exhibit dysregulation of vagal networks which normally synchronize the EEG, protect against arrhythmias and preserve visceral metabolism (15).

Both emotional and visceral reflex systems are sites of action of the secretin and oxytocin families of peptides and the stress factor CRH. Secretin is co-synthesized with or interacts with monoamines in

both the periphery and areas of the CNS, such as the viscera and the sympathetic ganglia (16). An example of visceral effect on cerebellar function is the feeling of hunger associated with significantly increased cerebral blood flow in cerebellum (17) and along polysynaptic projection sites in thalamus, hypothalamus, and cortical domains in limbic lobe including visceral orbitofrontal and insular association cortices (18).

Secretin neurons localize to several brain regions that are closely connected to the cerebellum, such as the hypothalamus, which act together to coordinate a wide range of activities, including behavioral and autonomic reflex control of visceral organ system response patterns (19–21). Secretinergic processes in paraventricular and preoptic hypothalamic nuclei are implicated in neurohumoral mechanisms related to blood-brain barrier functions (4). Primitive peptidergic cells, such as cells containing secretin and oxytocin immunoreactivity, appose ependyma and the walls of cerebral microvessels. These findings suggest a role in central chemo-sensitivity involved in the detection and rapid responses to changes in the chemical composition of CSF and blood. The secretin receptor is a G-protein-coupled receptor. A newly identified function of G-protein-coupled receptors is potential sensing of environmental cues during cerebellar histogenesis (22). This newly reported function is important to the current review of secretin as a neuromodulator in the cerebellum.

Our interest in secretin includes another neuropeptide that is involved in the modulation of gut function, oxytocin. The actions of secretin and oxytocin extend beyond the cerebellum to include resolution of visceral inflammation, together with its neurological manifestations in multiple sites (23). We have proposed that secretin may be critical to stress-responsivity/adaptation and to learning and memory. Secretin may also act as a neuromodulator in many brain regions other than the cerebellum. In this way secretin may be similar to other neuromodulators such as oxytocin. Secretin modulates both GABA and monoaminergic neurotransmitter systems, which exert influence over brain and spinal cord segments and over visceral organ systems function (2). Consequently, conditions associated with disruption in secretin modulation in the limbic system might also be associated with evidence of pathology in the gastrointestinal (GI) tract.

Implications for research and treatment of autism

Yung's review demonstrates on multiple levels the way that cerebellar secretin function is potentially related to autism and other developmental disorders. At the cellular level, secretin may be a 'retrograde