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Early life experience shapes the functional organization of stress-responsive visceral circuits

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ABSTRACT

Emotions are closely tied to changes in autonomic (i.e., visceral motor) function, and interoceptive sensory feedback from body to brain exerts powerful modulatory control over motivation, affect, and stress responsiveness. This manuscript reviews evidence that early life experience can shape the structure and function of central visceral circuits that underlie behavioral and physiological responses to emotive and stressful events. The review begins with a general discussion of descending autonomic and ascending visceral sensory pathways within the brain, and then summarizes what is known about the postnatal development of these central visceral circuits in rats. Evidence is then presented to support the view that early life experience, particularly maternal care, can modify the developmental assembly and structure of these circuits in a way that impacts later stress responsiveness and emotional behavior. The review concludes by presenting a working hypothesis that endogenous cholecystokinin signaling and subsequent recruitment of gastric vagal sensory inputs to the caudal brainstem may be an important mechanism by which maternal care influences visceral circuit development in rat pups. Early life experience may contribute to meaningful individual differences in emotionality and stress responsiveness by shaping the postnatal developmental trajectory of central visceral circuits.

1. Introduction

The importance of visceral and emotional functions in health and disease is well recognized. Emotions are closely tied to changes in autonomic outflow to the viscera, and interoceptive sensory feedback from body to brain exerts powerful modulatory control over motivation, affect, and emotional learning. Indeed, central visceral and emotional neural circuits are largely coextensive [1–8]. However, only limited research has been directed towards understanding how visceral and emotional neural control circuits are shaped by developmental events that are known to profoundly impact later emotionality and stress responsiveness in humans and animals [9–14]. This review examines how early life experience might shape the development of central visceral circuits by considering the special impact of maternal care received by rat pups during the first one to two weeks of postnatal life.

The mammalian brain exhibits a high degree of circuit plasticity during early development, and neural activity during this "sensitive period" of development can promote life-long changes in the way that neural circuits assemble and function later in life. We have shown that central pre-autonomic circuits undergo significant synaptic assembly and functional maturation in rats during the first two weeks of postnatal life, as do the largely overlapping circuits that receive interoceptive feedback from the body [15]. This developmental timeframe represents a potentially sensitive period for the synaptic assembly of visceral neural circuits, which are known to figure prominently in adult stress responsiveness, affect, and the physiological expression of emotion. Indeed, a growing body of work supports the view that early life experience impacts later emotionality and stress responsiveness in rats and other mammalian species, including humans [9–14,16–19]. A core thesis emerging from this work is that an organism's behavioral and physiological responses to the world are derived from interactions among its genetic heritage (including sex), early maternal care, and individual life history. In laboratory situations in which these factors can be controlled, animals raised in environments that are characterized by unusual maternal care (e.g., enhanced or disorganized) during the first one or two weeks of postnatal life will, as adults, display unusual behavioral and physiological responses to emotive and stressful stimuli. Further, laboratory models that alter the maternal care received by rat pups appear to impact their adult emotionality and stress responsiveness in a sexually dimorphic manner [20–26].

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1.1. Central visceral and emotional circuits are anatomically coextensive

William James proposed that emotional feelings represent the perceptual consequences of sensory feedback from the body that occur during and after stimulus-evoked bodily responses [27]. The core of James' theory persists today amid mounting evidence that visceral functions and interoceptive feedback about these functions are intimately associated with emotional and cognitive neurobehavioral systems [5,28–30]. Our research group subscribes to the view that emotions arise from bodily responses to real and anticipated challenges and opportunities to which the organism is exposed. The emotional responses are both innate and learned [31–33], and are supported by neural processing within brainstem, hypothalamic, limbic, and cortical circuits.

Viscerosensory signals provide continuous feedback to the organism about homeostatic balance and emotional status. Real or perceived threats to these functional states elicit a constellation of adaptive physiological and behavioral stress responses, some of which depend on noradrenergic (NA) and corticotropin releasing factor (CRF) signaling in the hypothalamus and limbic forebrain [34–40]. Recruitment of highly interacting central NA and CRF systems can occur as a result of markedly different precipitating events, including threats arising from the environment, such as the odor of a predator, or signals arising from within the body, such as visceral malaise. Stress responses can be innate or conditioned through learning [31–33], but they always include endocrine and autonomic adjustments that alter internal visceral functions. Interoceptive feedback about these altered functions is delivered via ascending NA pathways from the caudal medulla to forebrain targets that contain CRF neurons and are thought to participate in stress-related aspects of motivated behavior and affect [41]. These forebrain targets include the paraventricular nucleus of the hypothalamus (PVN), central nucleus of the amygdala (CeA), and bed nucleus of the stria terminalis (BNST). Indeed, CRF neuronal activity in these regions is closely regulated by NA inputs [cf. [41–43]] that arise primarily from viscerosensory regions of the caudal medulla, and NA/CRF interactions are strongly implicated in stress and emotional responsiveness that is sensitive to the effects of early life experience [44].

The PVN, medial preoptic area (MePO), lateral hypothalamus (LHA), CeA, nucleus accumbens (NAcc), BNST, insular cortex (IC), and medial prefrontal cortex (mPFC) serve as principal gateways for septohippocampal and cortical influences over bodily responses that include endocrine, autonomic, and somatic components [45–49] (see Fig. 1). Although most interoceptive signals never reach conscious awareness [50], sensory information regarding bodily state is delivered to these diencephalic and telencephalic regions to participate in the control of physiological and behavioral outflow, thereby biasing emotional and cognitive function and guiding ongoing and future motivated behavior [1,2,29,30,51]. Thus, factors that impact the developmental assembly and functional organization of central visceral circuits should impact emotionality and stress responsiveness.

1.2. Overview of central visceral circuits

The autonomic nervous system modifies visceral functions to meet the demands of immediate or anticipated changes in the organism's internal and external environments. Autonomic outputs are strongly modulated by limbic and cortical sites that drive complex and nuanced visceral reactions to diverse threats and opportunities, including reactions based on past experience [52]. In all cases, adjustment of visceral output is highly influenced by interoceptive feedback. Indeed, visceral motor and sensory pathways are largely reciprocal, as evidenced by results from anterograde and retrograde tract-tracing studies [53–55].

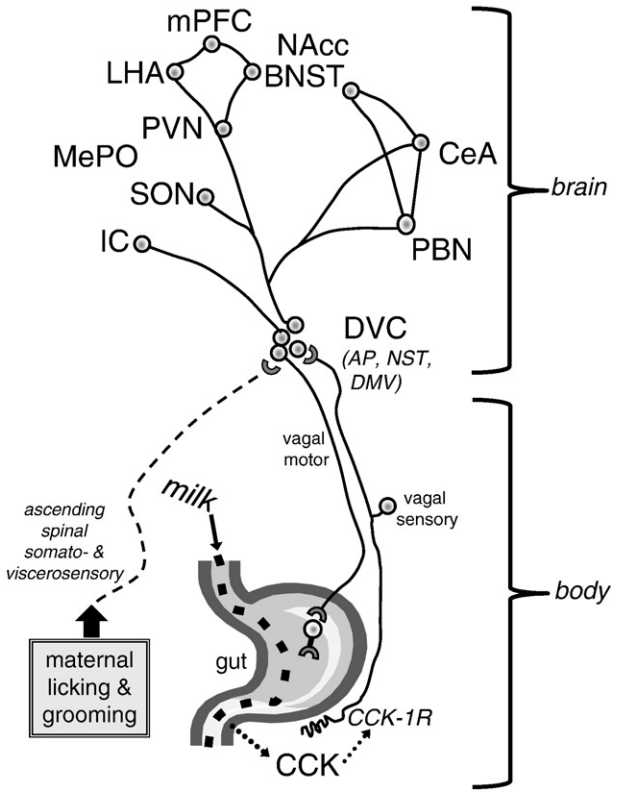

Fig. 1. Endogenous CCK released from the gut during milk digestion in neonatal rats activates vagal sensory inputs to the caudal medulla (DVC) through a CCK-1 receptor-mediated mechanism. We hypothesize that vagal sensory signals can interact within the DVC with other somatosensory and visceral sensory signals ascending from the spinal cord via the spino-solitary tract, including signals generated by maternal licking and grooming of the rat pup. These signals may thereby modulate the functional development of ascending and reciprocated descending projections between the DVC and hypothalamic and limbic forebrain regions that modulate physiological and behavioral responses of the animal to its internal and external environments. Circles and lines are meant to represent key circuit nodes and connections among them, although the representation is not all-inclusive. SON, supraoptic nucleus of hypothalamus; other abbreviations as in the text.

The caudal medullary dorsal vagal complex (DVC) is a critical central node in both descending visceral motor and ascending interoceptive feedback pathways [56]. The DVC comprises the dorsal motor nucleus of the vagus (DMV), nucleus of the solitary tract (NST), and area postrema (AP). DMV preganglionic neurons provide parasympathetic outflow to multiple thoracic and abdominal visceral targets, and NST neurons receive direct and relayed synaptic input from vagal, glossopharyngeal, trigeminal, facial, and spinal somatosensory and viscerosensory afferents. Thus, the NST receives multidimensional sensory feedback from the entire body. The AP and a significant portion of the caudal medial NST contain fenestrated capillaries, permitting local parenchymal access by blood-borne factors (e.g., toxins, cytokines, hormones, osmolytes) that can affect local neural activity. Descending pathways from the hypothalamus and limbic forebrain to the DVC allow emotional stimuli and cognitive events to shape autonomic outflow, and reciprocal ascending pathways provide a route through which sensory feedback from the body can modulate stress hormone release (i.e., via the hypothalamic-pituitary-adrenal (HPA) axis), direct motivated behavior, shape emotional appraisals, and alter cognitive processing.

1.3. Descending visceral motor pathways

Our current view of how central pre-autonomic visceral circuits are organized owes much to the results of studies using neurotropic α-herpesviruses for retrograde transneuronal tracing of multisynaptic