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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].

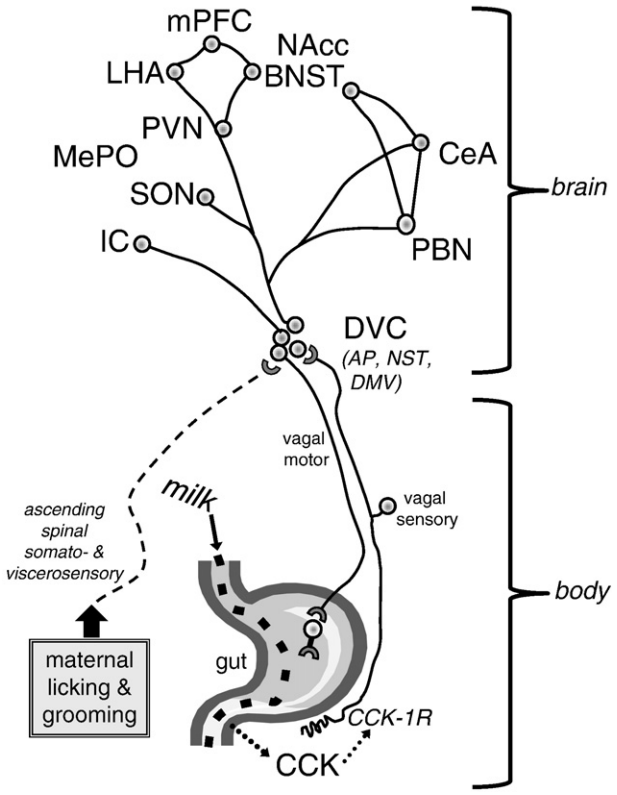

Fig. 1. Endogenous CCK released from the gut during milk digestion in neonatal rats activates vagal sensory inputs to the caudal medulla (DVC) through a CCK-1 receptor-mediated mechanism. We hypothesize that vagal sensory signals can interact within the DVC with other somatosensory and visceral sensory 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

central circuits [4,57–61]. Most of these studies have been conducted in adult rats, using attenuated vaccine strains of pseudorabies virus (PRV; a swine α-herpesvirus) that move selectively across synapses in the retrograde direction. For example, the Bartha strain of PRV [62] injected into the wall of the stomach [54,63,64] initially infects sympathetic and parasympathetic preganglionic motor neurons in the spinal cord and DVC, respectively, and subsequently is transported retrogradely and transneuronally to infect pre-autonomic neurons within circumscribed brainstem and forebrain regions. Central PRV transport from inoculated visceral targets that receive only sympathetic inputs (e.g., adrenal medulla, kidney, spleen) identifies essentially the same sets of medullary, pontine, midbrain, and diencephalic structures as are labeled by retrograde transport of classical tracers from different spinal levels of the sympathetic preganglionic column [65–68]. These structures include several hypothalamic nuclei (e.g., PVN and LHA), periaqueductal gray, locus coeruleus, Barrington's nucleus, ventromedial and ventrolateral pontine and medullary reticular formation, raphe nuclei, and the caudal medial NST. After similar post-inoculation intervals, PRV transport from viscera that receive both sympathetic and parasympathetic innervation (e.g., the wall of the stomach) identifies similar pre-autonomic regions of the brainstem and hypothalamus; however, the additional involvement of parasympathetic DVC neurons leads to additional infection of neurons within the CeA, BNST, IC, and mPFC [54,63,64] that are not similarly infected via sympathetic pathways. PRV tracing is uniquely suited for demonstrating, within a single animal, synaptic connections among neurons that occupy anatomically distinct nodes of multisynaptic, functionally-linked circuits [58].

1.4. Ascending visceral sensory pathways

Interoceptive information is relayed from body to brain along neural pathways that form largely reciprocal inputs to the same diencephalic and telencephalic regions that control visceral motor outflow [55,69] (see Fig. 1). Collateral projections from spinothalamic and dorsal column pathways merge with other ascending pathways that access the forebrain by relaying in the NST, reticular formation, and pontine parabrachial nucleus (PBN) [50,70–75]. Since most spinal and cranial nerve visceral afferent pathways include a primary or collateral synaptic relay in the NST, analysis of the central projections of NST neurons effectively reveals the principal brainstem and forebrain targets of viscerosensory signaling pathways [76–78]. Neurons in the caudal visceral portion of the NST project to the ventrolateral medullary reticular formation (VLM), lateral PBN, PVN, LHA, CeA, and BNST. These projections are primarily catecholaminergic, arising from noradrenergic A2 and adrenergic C2 neurons whose cell bodies occupy the NST. For simplicity, these neurons will be referred to collectively as "noradrenergic" (NA) because they all are immunoreactive for dopamine-β-hydroxylase (DbH), the enzyme that converts dopamine to norepinephrine. Viscerosensory signals transmitted through the NST also recruit a parallel ascending pathway arising from NA neurons in the caudal VLM (A1 and C1 cell groups). Ascending NA projections participate in recruiting hypothalamic and limbic forebrain neurons during stress responses and emotional learning in adult rats [79–83]. The brain NA system is activated by stress, and modulates the activity of forebrain regions involved in behavioral and neuroendocrine output, including the PVN, CeA, and anterolateral BNST. NA inputs to these regions are implicated in behavioral and hormonal stress responses [84–86] and are sensitive to the effects of early maternal care [84]. It should be noted that hindbrain NA neurons co-express multiple neurotransmitter/neuromodulator molecules (cf. [87]), and so future work should consider the potential role of other signaling pathways that are recruited as a result of activating these neurons.

2. Postnatal development of central visceral circuits

Vagal sensory input to the DVC and motor output to the gastrointestinal tract are established before birth in rats [88,89]. However, synaptic density within the DVC continues to increase over a protracted postnatal period [90–93]. Significant changes in glutamatergic and GABAergic transmission and local network properties within the DVC also occur postnatally [90,94,95], which contribute to the postnatal maturation of autonomic functions. For example, cardiac baroreceptor reflexes, which relay through the NST, are immature during the first postnatal week in rats [96,97], and spinobulbospinal reflexes subserving micturition and defecation do not emerge until the third postnatal week [98]. Descending corticobulbar projection systems also become increasingly myelinated and continue to establish new synaptic connections with brainstem target neurons during the same developmental period [54,99–101]. Collectively, these findings are consistent with our transneuronal PRV tracing results in neonatal rats, which indicate that diencephalic and telencephalic inputs to gastric DVC neurons are largely absent at birth and emerge gradually over the first two weeks postnatal [54,102,103]. Those studies demonstrated that descending pre-autonomic inputs from the hypothalamus, CeA, BNST, and visceral cortices reach the DVC between birth and P6, depending on their origin, but that the projections continue to mature postnatally. Indeed, many of these descending inputs do not establish synaptic connections within the rat DVC until the second postnatal week. As described below (Sections 2.1 and 2.2), the gradual maturation of central visceral circuits appears to underlie the postnatal maturation of behavioral and physiological responses to stressful events.

2.1. Postnatal maturation of dehydration anorexia

Dehydration anorexia provides an interesting example of how postnatal maturation of central visceral pathways corresponds with maturation of behavioral responses to an interoceptive challenge. Centrally-mediated responses to plasma hyperosmolality in adult rats include compensatory drinking [104], neurohypophyseal secretion of oxytocin and vasopressin [105], inhibition of vagally-mediated gastric motility and emptying [106,107], and inhibition of food intake [106]. The first two responses also occur in neonatal rats [108–110], whereas the latter response, termed "dehydration anorexia", does not emerge until after the first 2 weeks of postnatal development [109,111]. The mechanisms that underlie the postnatal emergence of dehydration anorexia in rats may be related to delayed maturation of osmotic influences on neural signaling within the hindbrain DVC. This idea is supported by observations that only a subset of hindbrain regions that are activated to express Fos in adult rats after acute osmotic dehydration treatment are similarly activated in 2-day-old rats, including a lack of dehydration-induced Fos within the neonatal NST [112]. Conversely, prominent NST Fos expression occurs in adult rats after osmotic dehydration and other treatments that inhibit both feeding and gastric motility [112,113]. The lack of NST Fos expression in dehydrated 2-day-old rats suggests that plasma hyperosmolality does not activate NST neurons in neonates, which led to the prediction that acute dehydration would not inhibit gastric emptying in neonatal rats, as it does in adult rats. This prediction was later found to be correct: an inhibitory effect of dehydration on gastric emptying emerges in rats between postnatal days 11 and 19, the same developmental period during which osmotic dehydration begins to inhibit rather than stimulate independent ingestion in rat pups [114].

These results point to an overlap between the functional maturation of central circuits that mediate dehydration-induced inhibition of gastric motility and emptying, and those that mediate inhibition of food intake. It is possible that these circuits share common structural features. For example, the ontogeny of dehydration-induced inhibition of both feeding and gastric emptying might be related to the postnatal maturation of central oxytocin (OT)-containing neural pathways.

Magnocellular and parvocellular OT neurons in the PVN are activated by osmotic dehydration in adult and neonatal rats [112], and central OT signaling is implicated in dehydration anorexia in adult rats [115]. A subset of hypothalamic OT neurons projects to the DVC in adult rats [116,117], and these projections play a physiologically important role in hypothalamic inhibition of vagally-mediated gastric motility [118]. Considered together, these findings suggest that central OT pathways contribute to both the hypophagic and gastric inhibitory effects of osmotic dehydration in adult rats. Conversely, central OT-containing pathways (including OT inputs to the DVC) are quite immature in neonatal rats, becoming gradually adult-like between 2 and 3 weeks postnatal [103]. Thus, postnatal maturation of central OT pathways may at least partially support the postnatal onset of dehydration-induced hypophagia and inhibition of gastric emptying.

2.2. The postnatal "stress hyporesponsive period"

The first 2–3 postnatal weeks of life correspond to a so-called "stress hyporesponsive period" that is characterized by reduced or absent HPA axis responses to many stimuli that robustly activate the HPA axis in adult rats. NA inputs to the medial parvocellular PVN provide important control over the activity of CRF-containing neurons at the apex of the HPA axis [37,39,119–122], and so immaturity of ascending NA viscerosensory pathways likely contributes to the documented hyporesponsiveness of CRF neurons to interoceptive stimuli in neonatal rats [123–127]. DbH fiber immunolabeling increases progressively in the rat PVN after postnatal day (P)1, with adult-like levels achieved by the end of the third postnatal week [127]. Functional immaturity of ascending viscerosensory pathways also has been demonstrated by analyzing neural Fos expression patterns in 2-day-old rats after systemic administration of cholecystokinin octapeptide (CCK) [128]. In striking contrast to results in adult rats, CCK treatment in 2-day-old rats does not activate Fos expression in the hypothalamus or other forebrain regions, and does not stimulate pituitary hormone release [128], consistent with other evidence for delayed postnatal maturation of ascending viscerosensory projections from the NST and VLM [54] to the hypothalamus and limbic forebrain [126,129–133]. Later work in our laboratory also revealed significant postnatal maturation of central Fos responses to another interoceptive challenge, systemically administered lithium chloride (LiCl) [126].

The findings summarized above support the view that central visceral circuits are structurally and functionally immature in neonatal rats. Thus, these circuits may exhibit plasticity as they assemble during their developmentally-defined sensitive period. Highly specialized mechanisms are crucial for the initial establishment of postsynaptic specializations during synaptogenesis, and for activity-related changes in synaptic strength that underlie experience-dependent plasticity [134]. By analogy with other CNS systems, evoked neural activity within visceral circuits should shape ongoing synapse formation during the first two weeks of postnatal life.

3. Early experience modifies emotionality and stress responsiveness

Several model systems have been used to study the effects of early life experience on adult emotionality and stress responsiveness, including repeated daily episodes of brief (e.g., 15 min; MS15) or more extended (e.g., 180 min; MS180) periods of maternal separation in order to manipulate maternal care received by rat pups during the first two postnatal weeks [135]. Maternal interactions with rat pups generate interoceptive signals that include olfactory, thermal, metabolic, hydrational, gastrointestinal, tactile, and hormonal components [136,137]. Perhaps paradoxically, the mild nest disruption inherent to the brief daily maternal separation paradigm (MS15) serves to significantly *increase* the amount of time that dams spend each day in active contact with their pups, including more time spent licking, grooming, and actively nursing them [14,138,139] compared to the behavior of dams that are not separated from their pups. Adult rats with a developmental history of daily MS15 during the first two weeks of postnatal life are less anxious in temperament and less behaviorally and hormonally responsive to laboratory stress paradigms compared to rats that were not separated from their dams during postnatal development [21,135,140–144]. However, and in sharp contrast to the increased maternal care elicited by MS15, rat pups exposed to daily MS180 during the first two weeks postnatal receive cumulatively *less* "high quality," active maternal care each day compared to pups in either MS15 or non-separated control litters [14,138,139,143,144]. Mature rats with a developmental history of MS180 generally are more anxious and hyper-responsive to stress as adults compared to rats with a developmental history of MS15 or no separation [17,135,145].

The long-term effects of MS15 and MS180 appear to originate from the differential antecedent effects of these manipulations on tactile aspects of maternal behavior. In non-separated control litters, these forms of maternal behavior, such as licking and grooming, are normally distributed across dams and litters [138,139]. Natural variations in maternal care received by pups in non-manipulated litters are correlated with differences in adult stress responsiveness [16,146,147], suggesting that relatively subtle alterations in early experience can significantly impact neural circuit development. As a result, non-separated litters represent a group that receives more variable maternal care compared to MS15 or MS180 litters; therefore, data from non-separated control litters tend to be more variable [139], and the most consistent experimental differences are often between rats raised in MS15 and MS180 litters [142]. Macrí, Würbel and colleagues [142–144] have effectively argued that active maternal care received by pups cannot entirely account for differences in their later endocrine and behavioral responsiveness to stressful/fearful events. Instead, maternal care received by pups appears to interact with maternal separation to exert relatively independent and opposing effects on the offspring, such that increased maternal care may act to buffer the adverse consequences of long separations [143].

4. Early experience modifies visceral circuit assembly

It has always been assumed that the effects of early experience on life-long emotionality and stress responsiveness involve epigenetic modification of CNS systems [17,148–151]. The long-term consequences of MS15 and MS180 on behavioral and physiological responses to stress are at least partially mediated by early experience-dependent alterations of central CRF signaling pathways and glucocorticoid receptors involved in negative feedback control over the HPA axis [12,17,140,152–158]. Most studies have focused on the neuroendocrine effects of MS15 and MS180, particularly alterations in the HPA axis that shape hormonal responses to acute and chronic stress. Far less attention has been paid to the potential impact of early life experience on adult visceral motor responses to stress, or on the neural pathways that relay sensory feedback about visceral responses to the brain. For example, adult rats with a developmental history of MS180 exhibit visceral hypersensitivity and are more prone to stress-induced intestinal mucosal dysfunction [155,159–162]. Sex-specific alterations in adult baseline mean arterial blood pressure and hypoxic ventilatory responses in MS180 rats are at least partly due to enhanced responsiveness of the phrenic and carotid sinus nerves [163–166].

4.1. Postnatal plasticity of visceral motor circuits

Based on anatomical and functional findings summarized in preceding sections, we hypothesized that experimental manipulation of early maternal care (via MS15 and/or MS180) would alter the ongoing developmental assembly of central visceral circuits in rat pups, thereby providing a potential structural correlate for early

experience-dependent effects on later physiological and behavioral responsiveness to emotionally evocative stimuli. To test this hypothesis, we traced central visceral circuit development in neonatal rats exposed to MS15 or MS180, using synapse-dependent retrograde transneuronal transport of PRV from the stomach wall [167]. Previous PRV tracing work in non-maternally separated rat pups had demonstrated that the first ten days of postnatal life represent a potential sensitive period of development, characterized by progressive synaptic assembly of central pre-autonomic circuits [54,102]. To study the effects of early life experience on ongoing circuit development and synaptic assembly, rat pups from each MS group were injected with PRV on P8 and perfused on P10, during the course of daily MS15 or MS180 [167]. Quantitative analysis of central PRV transneuronal transport in pups from non-separated control litters confirmed our previous observations of age-dependent assembly of hypothalamic, limbic, and cortical inputs to autonomic motor neurons [54,102]. Strikingly, however, circuit assembly was significantly altered in MS15 and MS180 pups, in which fewer neurons in the LHA, certain PVN subregions, CeA, BNST, and visceral cortices (mPFC, IC) were transneuronally labeled compared to labeling in age-matched controls [167]. Rather surprisingly, reductions in hypothalamic and limbic forebrain transneuronal infection were similar in MS15 and MS180 pups, and no sex differences were apparent. It is important to note, however, that these PRV tracing analyses were limited to a single early developmental time point (i.e., P8/P10) within ongoing circuit assembly. The results suggest that daily MS15 and MS180 manipulations exert a shared ability to delay the ongoing assembly of central visceral circuits during early postnatal development in both male and female rat pups; potentially, the daily handling/nest disruption intrinsic to both MS15 and MS180 could underlie this shared effect. Alternatively, or in addition, the surprisingly similar results that we obtained in 10-day old MS15 and MS180 pups [167] could have been due to the lack of pup isolation from littermates during daily MS180 treatment (e.g., see [144]). We subsequently have discovered that isolation is necessary for the ability of MS180 to increase anxiety-like behavior in the elevated plus maze in our experimental environment (unpublished observations), perhaps because isolation further reduces tactile and other sensory stimulation received by pups during the daily MS period. Thus, the MS180 group of pups used in our neonatal virus tracing study might not have grown up to exhibit the expected behavioral and endocrine phenotype.

It is of considerable interest to determine how early alterations in central pre-autonomic control circuits are manifested later in life, after synaptic assembly is complete and the circuits presumably are less plastic. Our recent findings in post-weaning juvenile rats (~P30) indicate that rats exposed to MS15 during the first 2 weeks of life display significantly enhanced transneuronal PRV labeling within pre-autonomic regions of the PVN compared to labeling in rats raised in non-separated control litters [168]. These results suggest that the reduction seen in neonatal MS15 rats reflects a delay in the developmental assembly of preautonomic circuits, rather than a permanent reduction in circuit strength. In ongoing research we are working to determine whether our new model for MS180 (i.e., incorporating pup isolation from littermates during each daily separation period) also promotes long-lasting effects on the structural organization of central visceral circuits.

4.2. Postnatal plasticity of visceral sensory pathways

The early MS paradigm has been used to show that maternal care has a significant impact on stressor-evoked norepinephrine release in the adult rat PVN [84]. Further, this effect is associated with altered NA α2 autoreceptor binding in the caudal medullary DVC, suggesting altered negative feedback control over stress-responsive NA neurons [84] that are heavily involved in local coordination of vagal motor outflow [169–172] and other behavioral functions, such as inhibition of food intake [53,81,173,174]. NA neurons within the DVC also are critically involved in relaying visceral sensory feedback to the PVN and BNST to initiate and modulate HPA axis responses to a variety of stressors [81,83,175,176]. This ascending NA projection pathway undergoes significant structural and functional maturation during the first two weeks postnatal [12,127,177], the same period during which visceral motor circuits are developing (discussed above). We also have demonstrated that DbH-positive NA axon terminals form appositions and synapses with pre-autonomic PVN neurons that were transneuronally and retrogradely labeled with PRV from the stomach wall in adult rats [178]. Thus, alteration of ascending NA pathways could contribute to experience-dependent differences in the effect of stressful and emotive stimuli on both endocrine (i.e., HPA axis) and pre-autonomic PVN functions, and thus, to differences in central neural, physiological, behavioral responsiveness to stress.

To test this idea, we examined whether MS15 and/or MS180 might alter the later ability of an interoceptive challenge to recruit central neural circuits that receive visceral sensory signals and generate stress responses [179]. We previously had demonstrated that central neural Fos responses to systemic LiCl matured during postnatal development [126], suggesting that the circuits underlying these responses might be susceptible to alteration by manipulating pups' early life experience during that period of maturation. Similar to previous reports in adult rats, adolescent rats (P35-45) with a developmental history of MS15 displayed less anxiety-like behavior on the elevated plus maze compared to control and MS180 rats [179]. MS15 rats tended to display fewer LiCl-activated neurons in most brain regions compared with rats in the other two rearing groups. The ability of MS15 to reduce central neural activation in rats after LiCl treatment may reflect, in a more general way, how early life experience can modulate later physiological and behavioral responses to homeostatic challenge. More recent work in our laboratory has extended these findings by demonstrating that MS15 also attenuates the ability of restraint stress to activate NA neurons within the DVC in juvenile rats [180].

5. How might maternal care shape central visceral circuit assembly?

Although the physiological effects of MS15 and/or MS180 on rat pups have not been rigorously examined, the available evidence suggests that some effects occur rapidly [181]. Conversely, plasma corticosterone levels do not begin to increase until pups have been isolated for several hours [182]. Thus, daily MS180 is unlikely to activate the HPA axis of developing pups, although this possibility has not been rigorously examined. Plasma osmolality and glucose levels also do not change in pups during daily MS180, although hypovolemia emerges within 2–3 hrs of maternal separation in the youngest pups [183]. Most laboratories utilizing the MS180 paradigm use an incubator to maintain pup body temperature during maternal separation, so hypothermia is unlikely to play a significant role.

In premature incubator-isolated human infants, supplementing tactile stimulation promotes marked gains in body weight and behavioral development, improved habituation and motor control, and significantly enhanced sympatho–adrenal maturation [184]. Clinical studies have demonstrated that providing premature human infants with active and passive touch, including skin-to-skin "kangaroo care" [10,185,186], alleviates many of the adverse effects of sensory neglect on behavior and physiology. Perhaps these interventions are effective because they alter the development of visceral neural circuits. Factors related to the presence of milk in the gut also are likely to affect the postnatal assembly and functional organization of central visceral circuits, and these factors may interact with tactile stimulation in a way that is altered by MS15 and/or MS180. For example, the upper gastrointestinal tract contains significantly less milk at the end of a 3 hr maternal separation period compared to the beginning [187]. Hofer has demonstrated that the presence of milk in the gastrointestinal tract potently modulates the activity of cardiac visceral sensory and motor pathways in neonatal

rats, supporting his view that milk is a physiological regulator of early autonomic activity and balance [97]. Suckling also provides significant somatosensory stimulation and exerts profound behavioral effects on newborn rat pups and human infants [188]. Maternally derived stimuli initiate simple somato–visceral and viscero–visceral reflexes in neonatal rat pups, including urination and defecation induced by anogenital licking by the dam.

Interestingly, intragastric infusion of milk (or other liquid nutrients) and patterned anogenital stimulation of rat pups can partially ameliorate the effects of prolonged maternal separation [189]. In this regard, it is particularly interesting that rat dams lick the perineal region of their male pups significantly more than that of their female pups [147], a factor which will alter the sensory stimulation received by pups and which may contribute to sex differences in how their central neural circuits assemble during the first two weeks postnatal. Thus, maternal nursing and licking of rat pups promote rhythms of activity within central visceral circuits during a sensitive period of development in which the nature and frequency of stimulation may affect the establishment and strength of synaptic connections.

Recall that the DVC receives direct sensory inputs from the vagus and other cranial nerves, and spinal sensory inputs via the spino–solitary tract. Within the DVC, signals related to gastrointestinal milk may interact with signals related to the amount and frequency of maternal licking and grooming received (Fig. 1). Visceral and somatosensory signals derived from maternal contact also may associate with increased or decreased levels of circulating factors such as growth hormone and CCK, both of which fall in pups during maternal separation and increase during and after feeding and/or tactile stimulation [190,191]. Such factors might participate in the interactive effects of milk and maternal touch to regulate visceral circuit development during early postnatal life [192–195]. CCK is released from intestinal mucosal secretory cells when nutrients, including those present in milk [196], are transferred from stomach to small intestine [197]. CCK subsequently binds to CCK-1 receptors expressed in the gastrointestinal tract and along vagal afferent fibers [198,199] to increase the activity of vagal sensory inputs to the medullary dorsal vagal complex [198]. CCK-1 receptors are especially abundant and widely distributed in the upper gastrointestinal tract in neonatal rats [200,201], in which intragastric milk and exogenously administered CCK have calming effects [202–204]. Further, functional antagonism of CCK-1 receptors with systemically administered devazepide counteracts the calming effects of milk infusion or normal suckling in rat pups [203,204].

We performed a study to examine whether the ability of MS15 to reduce later anxiety-like behavior in rats is at least partly due to increased gastrointestinal CCK release and signaling at CCK-1 receptors during the early postnatal period [205]. We predicted that rats with a developmental history of MS15 would display reduced anxiety-like behavior, as previously reported, and that this anxiolytic effect would be attenuated or reversed in rats in which daily MS15 was accompanied by systemic administration of devazepide to antagonize endogenous CCK-1 receptors. We reasoned that upon maternal reunion, increased somatosensory-related stimulation of pups by their dam promotes increased gastric emptying and delivery of existing milk from the pup's stomach into the duodenum (i.e., similar to maternal licking-induced micturition and defecation reflexes), contributing to an increase in plasma CCK levels that would increase gastrointestinal vagal sensory activation over the course of early postnatal development. As predicted, rats with a developmental history of MS15 displayed reduced anxiety-like behavior, and this behavioral phenotype was reversed in devazepide-treated rats [205]. It should be noted that devazepide does cross the blood–brain barrier [206], and so its pharmacological actions in our study cannot conclusively be ascribed only to reduced CCK-1 receptor signaling within gastrointestinal tissue and vagal sensory afferents. Nonetheless, our results support the view that endogenous CCK-1 receptor signaling in infants is a potential pathway through which maternal–pup interactions regulate the development and functional organization of emotional circuits that control anxiety-like behavior in the offspring.

6. Conclusion

Early postnatal life events can strongly influence the functional development of central neural systems that mediate the expression of behavioral, emotional, autonomic, and endocrine responses to stress. Although central visceral and emotional neural circuits are largely coextensive, relatively little research effort has been directed towards understanding how these circuits are shaped by developmental events that profoundly impact later emotionality and stress responsiveness. Experimental outcomes reviewed in this manuscript provide insight into the biological impact of early life experience on central circuits that respond to interoceptive and exteroceptive events, including events that elicit behavioral and physiological stress responses. Early life experience can shape the developmental trajectory of these neural circuits, leading to altered responses to internal and external sensory cues that may contribute to individual differences in emotionality and stress responsiveness.

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