Symposium

Central Network Dynamics Regulating Visceral and Humoral Functions

Rita J. Valentino,[1] Patrice Guyenet,[2] Xun Helen Hou,[3] and Melissa Herman[4]

[1]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania 19104, [2]University of Virginia, Charlottesville, Virginia 22908, [3]Harvard University, Boston, Massachusetts 02115, and [4]University of North Carolina, Chapel Hill, North Carolina 27599

The brain processes information from the periphery and regulates visceral and immune activity to maintain internal homeostasis, optimally respond to a dynamic external environment, and integrate these functions with ongoing behavior. In addition to its relevance for survival, this integration underlies pathology as evidenced by diseases exhibiting comorbid visceral and psychiatric symptoms. Advances in neuroanatomical mapping, genetically specific neuronal manipulation, and neural network recording are overcoming the challenges of dissecting complex circuits that underlie this integration and deciphering their function. Here we focus on reciprocal communication between the brain and urological, gastrointestinal, and immune systems. These studies are revealing how autonomic activity becomes integrated into behavior as part of a social strategy, how the brain regulates innate immunity in response to stress, and how drugs impact emotion and gastrointestinal function. These examples highlight the power of the functional organization of circuits at the interface of the brain and periphery.

Key words: **autonomic; gastrointestinal; immune; medulla; micturition; pons**

Introduction

The maintenance of homeostasis requires complex reciprocal communication between the brain and viscera as well as the immune system. This allows for information from these peripheral systems to be integrated with other sensory inputs to modulate the state of arousal, focus of attention, and executive function. This communication also allows the brain to regulate the autonomic nervous system that controls visceral and immune function in response to internal and environmental challenges. In addition to maintaining homeostasis, the same circuitry that underlies reciprocal communication between the brain and periphery also provides routes through which pathology at either end can adversely influence the other.

Elucidating the complex interplay between the brain and peripheral systems that is involved in the coordination of behavior with visceral activity requires the dissection of complex circuits and, in particular, the ability to specifically manipulate them and to record neural activity and visceral endpoints simultaneously under natural conditions. Tools developed over the last few years have enhanced our ability to achieve these goals and advanced our knowledge in this area. Here we provide examples of knowledge gained through these approaches that has led to a better understanding of how the brain and periphery interact and the importance of this interaction in health and disease.

The brain-bladder intersection and its role in social behavior and disease

The pontine micturition center (PMC), also referred to as Barrington's nucleus, is an integral component of a circuit that regulates the descending limb of the micturition reflex. PMC axonal projections extend to the lumbosacral spinal cord and terminate within the preganglionic parasympathetic nucleus that provides the parasympathetic input to the detrusor and distal colon (Loewy et al., 1979; Hida and Shimizu, 1982) (Fig. 1). PMC lesions disrupt the micturition reflex, whereas electrical or chemical stimulation of this region elicits bladder contractions and micturition, the act of passing urine (Barrington, 1925; Willette et al., 1988; Noto et al., 1989; Pavcovich and Valentino, 1995). Although the PMC is neurochemically heterogeneous, many neurons express the stress-related neuropeptide, corticotropin-releasing factor (CRF) (Vincent and Satoh, 1984; Valentino et al., 1994, 1996; Hou et al., 2016). This makes the PMC amenable for manipulation by genetically driven tools and provides an opportunity to probe this system with a much higher specificity than was previously allowed using lesions or chemical or electrical stimulation. The use of these tools is both validating and refining our views of the neurophysiology and function of micturition.

In male mice, the electrophysiological and molecular characterization of CRF-positive (CRF^+) PMC neurons reveals that they are distinct from their CRF-negative neighbors and

Received Aug. 17, 2017; revised Oct. 3, 2017; accepted Oct. 8, 2017.

This work was supported by Public Health Service Grants AG052780-01 to R.J.V., DK102367 to R.J.V., DK103086 to X.H.H., HL028785 to P.G., HL074011 to P.G., and AA023002 to M.H. Research on central mechanisms regulating context-dependent micturition was conducted in the laboratory of Dr. Bernardo Sabatini (Howard Hughes Medical Institute and Harvard Medical School, Boston, Massachusetts). Research on neural recordings in unanesthetized rats during cystometry was done by Dr. Anitha Manohar (Merck, West Point, Pennsylvania) in the Laboratory of R.J.V.

The authors declare no competing financial interests.

Correspondence should be addressed to Dr. Rita J. Valentino, Division of Neuroscience and Behavior, National Institute on Drug Abuse, 6001 Executive Blvd, Room 4269, MSC 9555, Bethesda, MD 20892-9555. E-mail: valentinorj@nida.nih.gov.

R. J. Valentino's current address: National Institute on Drug Abuse, 6001 Executive Blvd., Bethesda, MD 20892-9555.

X. H. Hou's current address: Columbia University, 701 W. 168 St., Hammer Bldg. Rm 510, New York, NY 10032.

DOI:10.1523/JNEUROSCI.1833-17.2017

 0270-6474/17/3710848-07$15.00/0

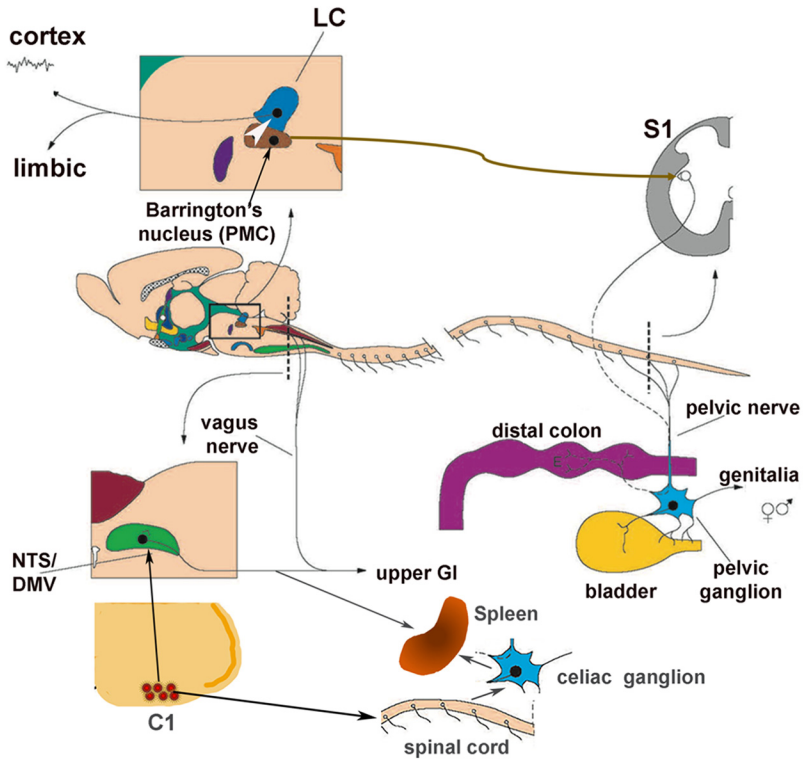

Figure 1. Schematic showing circuits linking specific brain nuclei with viscera that are discussed in this review. Based on dual retrograde labeling, PMC axons putatively branch to the nearby LC (white arrowhead) and to the parasympathetic column of preganglionic neurons in the lumbosacral spinal cord. The latter project through the pelvic nerve and major pelvic ganglion to regulate pelvic visceral activity, including micturition. The LC projects to the cortex and limbic nuclei, where it can function in central aspects of voiding behavior. The dorsal motor nucleus of the vagus (DMV, box at the bottom left with part of a transverse section through the dorsal medulla) innervates the upper gastrointestinal tract and spleen. C1 neurons in the ventrolateral medulla can regulate immune function through projections to spinal sympathetic ganglia that project to celiac/suprarenal ganglia that innervate the spleen. Modified with permission from (Pavcovich and Valentino, 1995).

that they are sacral cord-projecting glutamatergic neurons (Hou et al., 2016). Combining transgenic mouse lines with molecular tools enabled genetic control over urine output, and it was demonstrated with fiber photometry that the population activity of CRF$^+$ PMC neurons correlates with micturition (Hou et al., 2016). Selective activation of CRF$^+$ PMC neurons with light-activated cation channel channelrhodopsin-2 is sufficient to trigger bladder contractions. The fast time course of bladder contraction following light onset supports the hypothesis that glutamate release from CRF$^+$ PMC neurons in the spinal cord drives contraction. Conversely, reversible chemogenetic silencing of CRF$^+$ PMC neurons with hM4Di, an engineered Gi protein-coupled receptor, impairs micturition.

In addition to serving an essential physiological function of waste elimination, micturition plays an important role in social communication due to the distinguishing information about an animal's identity carried by the chemical components in urine (Yamaguchi et al., 1981; Singer et al., 1997; Hurst and Beynon, 2004). As a result, voiding behaviors that determine where and when adult animals micturate are tightly regulated by internal and external sensory inputs and can be altered by experience and context (Desjardins et al., 1973).

The interaction of olfactory cues and social rank regulates the pattern of micturition in male mice. The presence of estrous female urine in an open-field arena increased the frequency and changed the spatial distribution of micturition selectively in dominant male mice (Hou et al., 2016). That the average location of the urine spots was not predicted by the average location of the mouse supports the existence of a central circuit that actively regulates micturition in a social setting. Notably, social stress regulates micturition in an opposing manner in subordinate males, inhibiting micturition frequency to the extent of producing pathology (Desjardins et al., 1973; Henry et al., 1982; Wood et al., 2009).

CRF$^+$ PMC neurons receive input from multiple forebrain areas that can relay diverse promicturition and antimicturition signals (Hou et al., 2016). Whole-brain analysis of male mice reveals a widespread micturition regulatory network with a large degree of convergence onto ~500 CRF$^+$ PMC neurons. Candidate presynaptic neurons were found in cerebral cortices, olfactory relay nuclei, and hypothalamic and brainstem nuclei; among them are areas that process olfactory and social hierarchical information.

Rabies virus tracing in male mice identified a robust putative input to CRF$^+$ PMC neurons from the medial preoptic area (MPOA) (Hou et al., 2016). The MPOA is a heterogeneous structure previously shown to be connected to multiple regions involved in social behaviors (Simerly and Swanson, 1986, 1988; Simerly et al., 1986). MPOA neurons retrogradely labeled from the PMC are homogeneously GABAergic, and chemogenetic inhibition of GABAergic MPOA neurons altered micturition patterns and reduced differences in micturition between subordinate and dominant males, indicating that GABAergic MPOA neurons normally modulate micturition in the marking assay (Hou et al., 2016). These results are consistent with a model in which silencing inhibitory MPOA inputs disinhibits CRF$^+$/glutamatergic PMC neurons.

Together, these results in male mice indicate that CRF$^+$/glutamatergic neurons in the PMC comprise a brainstem command output that controls urine release. These neurons have the capacity, anatomically and functionally, to integrate promicturition and antimicturition inputs from relevant brain areas and transmit these signals into urine output, a process that exemplifies the integrative capacity of brainstem nuclei to regulate visceral activity and behavior. The whole-brain analysis of candidate input areas to CRF$^+$ PMC neurons in male mouse may reveal additional factors that regulate micturition. Future work involving a detailed intranucleus cell type and connectivity characterization of the PMC, combined with population recording and circuit perturbation, will reveal the neural mechanisms by which specific contextual cues, such as sensory stimuli, bladder pressure, social hierarchy and past experience, are integrated to regulate micturition.

The descending limb of the micturition reflex described above that regulates urine release must be coordinated with a central limb that regulates voiding behaviors that determine when and where micturition occurs. For micturition to occur in safe and socially appropriate environments, arousal must be elevated and attention focused on the visceral stimulus. Ongoing behavior unrelated to voiding must be interrupted and replaced by voiding

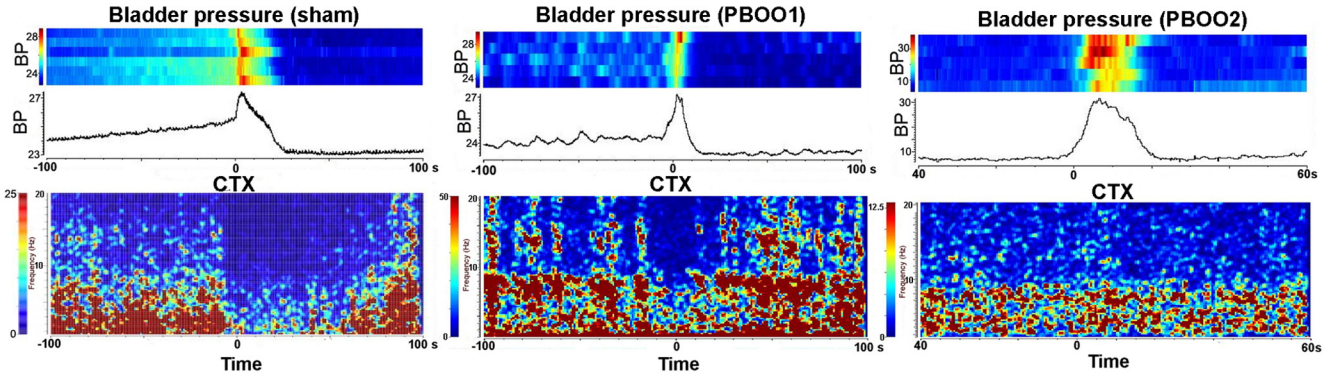

Figure 2. Relationship between bladder pressure and cortical (CTX) activity in rats exposed to partial bladder outlet obstruction (PBOO) or sham surgery. Middle, Mean bladder pressure over 5–6 micturition cycles and centered at the micturition threshold (time = 0). Heat map above each trace represents bladder pressure for each micturition cycle. For sham, bladder pressure increases gradually and uniformly up to micturition threshold. PBO01 shows nonmicturition contractions as sporadic episodes (lighter blue blocks interspersed within darker blue) that occur up to micturition threshold. PBO02 does not exhibit a gradual increase in pressure or nonvoiding contractions. Bottom, Corresponding heat maps represent the mean relative power in different EEG frequency bands (0–20 Hz, ordinate) over the same time period as the bladder pressure recording. In sham rats, a decrease in power in all frequencies (i.e., desynchronization) precedes the micturition threshold and is maintained. PBOO disrupts the relationship between bladder pressure and cortical EEG activity. PBO01 CTX activity exhibits greater power in higher frequencies (7–10 Hz and 14–15 Hz) that fluctuate like the contractions. CTX activity in PBO02 is desynchronized throughout the session, and increases in bladder pressure up to the micturition threshold are without further effect. Modified with permission from Rickenbacher et al., 2008).

behaviors that determine temporal and spatial aspects of micturition. All of this must occur in tune with changes in bladder pressure and before micturition. The norepinephrine-containing pontine nucleus, locus ceruleus (LC), is central in a circuit through which bladder sensations can be transmitted to the cortex (Valentino et al., 2011) (Fig. 1). The broad axonal projections arising from LC neurons densely innervate the cortex (Swanson and Hartman, 1976). In anesthetized rats, LC neurons are activated by relatively low magnitudes of bladder or distal colon distention, and this is associated with cortical desynchronization (Elam et al., 1986; Svensson, 1987; Page et al., 1992; Lechner et al., 1997). LC activation by salient sensory stimuli of diverse modalities has been demonstrated to precede the motor response of orientation to the stimulus (Aston-Jones and Bloom, 1981). Pelvic visceral information could be transmitted to the LC from the PMC, as a discrete population of PMC neurons are retrogradely labeled from the LC (Valentino et al., 1996). Alternatively, the periaqueductal gray area, which is hypothesized to relay information about urodynamic status to Barrington's nucleus, may also communicate bladder sensory information to the LC (Bajic et al., 2000; de Groat and Wickens, 2013).

Simultaneous recordings of LC single-unit activity, LC local field potentials, and prefrontal cortical local field potential activity during cystometry in unanesthetized rats are revealing the temporal relationship between urodynamic status and neural activity within different nodes of the pontine-cortical micturition circuit. Preliminary studies in female rats suggest that LC neurons consistently increase their tonic discharge rate 10–30 s before the point of peak bladder pressure and micturition. During this premicturition period, LC local field potential recordings reveal a shift from relatively high-amplitude, low-frequency activity to a prominent theta oscillation and increased LC-PFC coherence. This shift in LC network activity triggers activation of the PFC as indicated by a decrease in amplitude of power at all frequencies, typical of a desynchronized cortical EEG. The desynchronization of cortical activity before micturition has also been reported in male rats (Kiddoo et al., 2006; Rickenbacher et al., 2008). Because LC and cortical responses precede the onset of micturition, it is speculated that these changes in LC-cortical network activity serve to increase arousal and redirect behavior to facilitate appropriate voiding behaviors before urination.

The same network that underlies the adaptive viscero-behavioral response to bladder stimuli described above is also implicated in central symptoms of bladder disorders. Male rats that have surgery for partial bladder outlet obstruction, which has been used to model the partial obstruction that occurs in benign prostatic hypertrophy, develop abnormal urodynamic patterns (Rickenbacher et al., 2008). This model of chronic uropathology altered neuronal firing patterns throughout the pontine-cortical micturition pathway. By 2 weeks after surgery, both PMC and LC neurons became unresponsive to bladder distention, although baseline LC neuronal discharge was elevated above that in sham-operated controls, suggesting a state of hyperarousal in these animals. Consistent with this, from 1 to 4 weeks after surgery, the power spectrum of the cortical EEG shifted to the right toward higher frequencies, indicative of increased arousal, and this effect progressed with time after surgery. A cortical theta oscillation developed in many subjects, particularly those exhibiting nonmicturition contractions, and this appeared to be temporally correlated to the contractions, suggesting that it may be a cortical signature of urgency (Fig. 2). The theta oscillation is likely driven by LC hyperactivity because chemical lesioning of LC-cortical projections prevented its development while leaving the nonmicturition contractions intact. Notably, in this model of bladder pathology, the temporal relationship between bladder pressure and cortical activity becomes disrupted such that the cortical desynchronization that typically precedes micturition is diminished or is not apparent because the cortex is either desynchronized by default or is exhibiting prominent theta oscillations (Fig. 2). These neural alterations that develop in concert with urodynamic alterations in this model of chronic pathology may be the basis of central symptoms of this visceral disease. For example, increased LC tone that contributes to cortical theta oscillations and an enduring desynchronization of cortical EEG could underlie the sensation of urgency, sleep disruption, and anxiety that characterize lower urinary tract disorders (Kirby, 2000; Huang et al., 2017). Importantly, the loss of the cortical response that should precede the micturition event to initiate voiding behaviors may underlie the decreased sensation of bladder fullness that occurs in men with lower urinary tract symptoms and could contribute to enuresis (Griffiths, 1998). This example highlights how circuits that are the foundation of communication between

the brain and viscera support both ongoing physiological functions as well as the expression of comorbid cognitive and visceral symptoms. Dysfunctions of this circuit may be common to other pelvic visceral disorders that are characterized by both central and visceral symptoms, such as irritable bowel syndrome.

Acute stress and inflammation: role of the autonomic nervous system (ANS) and C1 neurons

The C1 neurons are catecholaminergic/glutamatergic/peptidergic cells located in the rostral ventrolateral medulla that regulate both divisions of the ANS via direct projections to preganglionic neurons (Abbott et al., 2013; Guyenet et al., 2013). During hypoxia, general anesthesia, or hypoglycemia, activation of the presympathetic C1 neurons has a homeostatic function that includes minimizing hypotension or restoring blood glucose (Madden et al., 2006; Wenker et al., 2017). C1 cell activation has an allostatic role during pain, fear, restraint, or exercise, increasing glycemia, blood pressure, and respiration (Barna et al., 2012; Chen et al., 2012; Guyenet et al., 2013; Burke et al., 2014; Zhao et al., 2017). The C1 cells may operate as a switchboard for the elaboration of autonomic response patterns. Subsets of presympathetic C1 neurons differentially activate specific groups of preganglionic neurons, thereby producing patterns of sympathetic nerve activation best suited to assist a given behavior or to mitigate the adverse effects of a given stressor (Guyenet et al., 2013). A subset of C1 neurons contribute to the activation of the hypothalamic-pituitary-adrenal axis via direct, and probably indirect, projections to the paraventricular hypothalamic nucleus (Tucker et al., 1987; Schiltz and Sawchenko, 2007). The C1 cells that innervate parasympathetic preganglionic neurons (Loewy et al., 1994; DePuy et al., 2013) must also shape the autonomic responses to stressors, but their exact contribution is unexplored. The activity of C1 neurons is reflexly regulated and under the control of nuclei distributed throughout the brain (Janig, 2006).

The ANS regulates innate immunity. For example, vagal parasympathetic efferent neurons are the efferent arm of an anti-inflammatory reflex mediated by the spleen (Pavlov and Tracey, 2017). Anti-inflammatory reflexes can also be elicited via the sympathetic system. In anesthetized rats, splanchnic nerve section enhances the production of TNFα elicited by lipopolysaccharide injection, suggesting that the production of this inflammatory cytokine is normally restrained by ongoing sympathetic tone (Martelli et al., 2014). Also, sympathetic hyperreflexia following high spinal cord lesions depresses the immune system of mice (Ueno et al., 2016). The central pathways mediating these reflexes are unexplored as are the brain structures that modulate them. In the remainder of this section, we summarize recent evidence that acute stress reduces inflammation and tissue damage via activation of C1 neurons and sympathetic nerves but independently of corticosterone release. This work was done in male mice using renal ischemia-reperfusion (IR) as a model of organ damage.

Renal IR carries a major risk of permanent injury to these organs; the damage is caused or at least exacerbated by inflammation (Inoue and Okusa, 2015). Restraint stress, 24 h before IR, substantially reduced renal damage in mice (Abe et al., 2017). This protective effect was transferable to naive mice by injecting splenocytes harvested from stressed mice and could also be induced by injection of CD4 splenic T cells harvested from control mice and incubated with noradrenaline *in vitro* (Abe et al., 2017). Protection against IR damage was also elicited by moderate optogenetic activation of C1 cells in conscious mice. The protective effect of restraint stress was greatly attenuated in mice with selective C1 cell lesions or if restraint was applied while C1 neurons were selectively inhibited (Abe et al., 2017). The protective effect of C1 stimulation disappeared after splenectomy or by silencing the ANS with a ganglionic blocker during C1 stimulation but could not be explained by corticosterone elevation. Finally, the protection persisted after subdiaphragmatic vagotomy. Thus, restraint stress activates a splenic anti-inflammatory mechanism that protects the kidneys from IR injury (Pavlov and Tracey, 2017). In this particular instance, the splenic noradrenergic innervation was activated predominantly via preganglionic sympathetic rather than parasympathetic neurons.

In short, acute stress activates C1 cells causing anti-inflammation and tissue protection. This effect, along with other potentially beneficial consequences of C1 cell stimulation, such as increased vigilance, cardiorespiratory and metabolic stimulation, presumably enhance the chances of surviving an injury.

Anti-inflammatory effects can be elicited by a host of seemingly unrelated interventions, such as stimulation of the vagal nerve, the auricular nerve or somatic nerve afferents via acupuncture (Inoue et al., 2016; Abe et al., 2017; Pavlov and Tracey, 2017). Vagal nerve stimulation attenuates selected signs (circulating cytokines) and symptoms (pain) of rheumatoid arthritis in humans, although the underlying mechanism is not completely elucidated (Koopman et al., 2016). It is possible that the discharge pattern produced by nerve stimulation is distinctly unphysiological and may be interpreted by the CNS as untoward regardless of its origin in the body. A shared effect of peripheral nerve stimulation could be the recruitment of C1 neurons with one of the consequences being activation of the splenic anti-inflammatory pathway via a sympathetic or vagal efferent route or both. In support of this speculation, C1 neurons receive most of their input from the pontomedullary reticular core and respond to innumerable noxious or innocuous stimuli, including restraint stress, infection (lipopolysaccharide, interleukin-1), hypoglycemia, hypotension, and electrical activation of subsets of vagal or somatic sensory afferents (Guyenet et al., 2013; Stornetta et al., 2016; Dempsey et al., 2017).

Nucleus tractus solitarius (NTS)-central amygdala circuitry: target of ethanol

Central regulation of gastric function occurs through sensory vagal afferent projections into the NTS, which synapse onto the dorsal motor nucleus of the vagus to regulate motor vagal efferent signals back to the gut (Travagli et al., 2006). Local $GABA_A$ receptor activity in this circuit is a critical regulator of gastric function, as $GABA_A$ receptor blockade in the NTS of male rats reduced gastric tone and motility (Herman et al., 2009). Gastric-projecting as well as unlabeled NTS neurons receive local GABAergic input that modulates vagal afferent transmission and NTS neuronal excitability in rats and mice (Davis et al., 2004; Glatzer et al., 2007; Herman et al., 2009, 2012). The NTS also makes reciprocal connections with the central amygdala (CeA) (Geerling and Loewy, 2006) and thus is poised to integrate peripheral viscero-sensory input with cognitive emotional state. This may be relevant to diseases with comorbid affective and gastrointestinal symptoms (Folks, 2004). However, little is known regarding how alterations in NTS circuitry contribute to neurobehavioral pathology. Here we discuss how ethanol can target this circuitry to influence gastric function and affect.

Given its role in peripheral gastric function, NTS circuits are vulnerable to the effects of ethanol through direct actions in the brain as well as direct effects on the gastrointestinal system. Acute ethanol has been shown to increase local inhibitory transmission and decrease the firing of the majority of NTS neurons (Aimino et

al., 2017). Acute ethanol has also been shown to increase c-fos expression in the NTS (Thiele et al., 1996). Preliminary data suggest that chronic intragastric administration of ethanol and acute withdrawal in male rats increase inhibitory transmission but also result in increased baseline excitability in NTS neurons, suggesting cell-type specific neuroadaptations and/or the recruitment of other signaling systems. Genetically selective manipulation of NTS neurons is necessary to dissect the effects of acute and chronic ethanol on specific components NTS circuitry.

Reciprocal projections link the NTS and the central nucleus of the amygdala (CeA) (Saper, 2002; Geerling and Loewy, 2006), and these are activated by visceral afferent stimulation (McDougall et al., 2017). The CeA functions as an integrative hub that converts emotionally relevant sensory information about the external environment and internal milieu into appropriate behavioral and physiological responses (Gilpin et al., 2015). Although the amygdala is involved in appetitive conditioning processes, it plays a major role in aversive conditioning and negative emotional states. It has been implicated in fear, the behavioral consequences of stress, and alcohol dependence. The CeA is primarily a GABAergic nucleus (Pitkänen and Amaral, 1994; Veinante and Freund-Mercier, 1998), and evidence suggests an involvement of neuroadaptations in CeA GABAergic transmission in the effects of acute ethanol and in the development of alcohol dependence (Roberto et al., 2004, 2010). Acute and chronic ethanol disinhibits CeA output neurons through effects on a local inhibitory microcircuit (Herman et al., 2013; Herman and Roberto., 2016; Herman et al., 2016). Chronic ethanol exposure increases ambient GABA in the CeA (Roberto et al., 2004), although the specific source of this GABA is not yet identified. Whereas attention has focused on forebrain afferents to the CeA (PFC and adjacent amygdala structures), the role of brainstem afferents, such as the NTS, has been relatively neglected.

Preliminary studies, examining the effects of acute and chronic ethanol on CeA-projecting NTS neurons from male rats, suggest that these neurons are under a significant amount of inhibitory control that is enhanced by ethanol exposure. Acute ethanol decreased the firing of most CeA-projecting NTS neurons, consistent with previous work (Aimino et al., 2017). Chronic ethanol increased the baseline inhibitory tone of CeA-projecting NTS neurons; however, this appeared to occur in parallel with a paradoxical increase in basal firing, suggesting the possibility of negative feedback and/or compensatory mechanisms. Collectively, these preliminary data suggest that acute and chronic ethanol exposure alters the function of the NTS and NTS-CeA circuits. Increased inhibitory tone in the NTS could dampen the impact of afferent signals important for the maintenance of physiological gastric control. Increased excitability of NTS neurons following chronic ethanol exposure would simultaneously result in reduced central control over the gastrointestinal system, via increased inhibition of dorsal motor nucleus of the vagus motor neurons, and increased inhibitory drive to the CeA. This has potentially negative consequences for the central control of gastric function and the relay of visceral input to the amygdala, which could collectively enhance the aversive outcomes of chronic ethanol exposure and contribute to the development of alcohol dependence.

Conclusions

In conclusion, here we highlighted examples of circuits that support the interdependence between the brain and specific peripheral organs, with the functional endpoint of one organ (spleen) being regulation of an immune response. These circuits allow for the integration of visceral information with ongoing multimodal sensory signals and the computation of a response that coordinates visceral activity with motor activity, behavior, and cognition. The examples presented here demonstrate how the ongoing activity of these circuits assures optimal functioning of the whole organism but can also be conduits for the synchronized expression of pathology at central and peripheral sites. Continuing advances in circuit dissection, manipulation, and neural network recordings will provide the necessary information to extend the brain atlas to the periphery.

References

Abbott SB, DePuy SD, Nguyen T, Coates MB, Stornetta RL, Guyenet PG (2013) Selective optogenetic activation of rostral ventrolateral medullary catecholaminergic neurons produces cardiorespiratory stimulation in conscious mice. J Neurosci 33:3164–3177. CrossRef Medline

Abe C, Inoue T, Inglis MA, Viar KE, Huang L, Ye H, Rosin DL, Stornetta RL, Okusa MD, Guyenet PG (2017) C1 neurons mediate a stress-induced anti-inflammatory reflex in mice. Nat Neurosci 20:700–707. CrossRef Medline

Aimino MA, Coker CR, Silberman Y (2017) Acute ethanol modulation of neurocircuit function in the nucleus of the tractus solitarius. Brain Res Bull. Advance online publication. Retrieved Jul. 29, 2017. doi: 10.1016/j.brainresbull.2017.07.019. CrossRef Medline

Aston-Jones G, Bloom FE (1981) Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J Neurosci 1:887–900. Medline

Bajic D, Proudfit HK, Van Bockstaele EJ (2000) Periaqueductal gray neurons monosynaptically innervate extranuclear noradrenergic dendrites in the rat pericoerulear region. J Comp Neurol 427:649–662. CrossRef Medline

Barna BF, Takakura AC, Moreira TS (2012) Pontomedullary and hypothalamic distribution of Fos-like immunoreactive neurons after acute exercise in rats. Neuroscience 212:120–130. CrossRef Medline

Barrington FJ (1925) The effect of lesion of the hind- and mid-brain on micturition in the cat. Q J Exp Physiol 15:81–102. CrossRef

Burke PG, Abbott SB, Coates MB, Viar KE, Stornetta RL, Guyenet PG (2014) Optogenetic stimulation of adrenergic C1 neurons causes sleep state-dependent cardiorespiratory stimulation and arousal with sighs in rats. Am J Respir Crit Care Med 190:1301–1310. CrossRef Medline

Chen D, Jancovski N, Bassi JK, Nguyen-Huu TP, Choong YT, Palma-Rigo K, Davern PJ, Gurley SB, Thomas WG, Head GA, Allen AM (2012) Angiotensin type 1A receptors in C1 neurons of the rostral ventrolateral medulla modulate the pressor response to aversive stress. J Neurosci 32:2051–2061. CrossRef Medline

Davis SF, Derbenev AV, Williams KW, Glatzer NR, Smith BN (2004) Excitatory and inhibitory local circuit input to the rat dorsal motor nucleus of the vagus originating from the nucleus tractus solitarius. Brain Res 1017:208–217. CrossRef Medline

de Groat WC, Wickens C (2013) Organization of the neural switching circuitry underlying reflex micturition. Acta Physiol 207:66–84. CrossRef Medline

Dempsey B, Le S, Turner A, Bokiniec P, Ramadas R, Bjaalie JG, Menuet C, Neve R, Allen AM, Goodchild AK, McMullan S (2017) Mapping and analysis of the connectome of sympathetic premotor neurons in the rostral ventrolateral medulla of the rat using a volumetric brain atlas. Front Neural Circuits 11:9. CrossRef Medline

DePuy SD, Stornetta RL, Bochorishvili G, Deisseroth K, Witten I, Coates M, Guyenet PG (2013) Glutamatergic neurotransmission between the C1 neurons and the parasympathetic preganglionic neurons of the dorsal motor nucleus of the vagus. J Neurosci 33:1486–1497. CrossRef Medline

Desjardins C, Maruniak JA, Bronson FH (1973) Social rank in house mice: differentiation revealed by ultraviolet visualization of urinary marking patterns. Science 182:939–941. CrossRef Medline

Elam M, Thorén T, Svensson TH (1986) Locus coeruleus neurons and sympathetic nerves: activation by visceral afferents. Brain Res 375:117–125. CrossRef Medline

Folks DG (2004) The interface of psychiatry and irritable bowel syndrome. Curr Psychiatry Rep 6:210–215. CrossRef Medline

Geerling JC, Loewy AD (2006) Aldosterone-sensitive neurons in the nucleus of the solitary tract: bidirectional connections with the central nucleus of the amygdala. J Comp Neurol 497:646–657. CrossRef Medline

Gilpin NW, Herman MA, Roberto M (2015) The central amygdala as an integrative hub for anxiety and alcohol use disorders. Biol Psychiatry 77:859–869. CrossRef Medline

Glatzer NR, Derbenev AV, Banfield BW, Smith BN (2007) Endomorphin-1 modulates intrinsic inhibition in the dorsal vagal complex. J Neurophysiol 98:1591–1599. CrossRef Medline

Griffiths D (1998) Clinical studies of cerebral and urinary tract function in elderly people with urinary incontinence. Behav Brain Res 92:151–155. CrossRef Medline

Guyenet PG, Stornetta RL, Bochorishvili G, DePuy SD, Burke PG, Abbott SB (2013) C1 neurons: the body's EMTs. Am J Physiol Regul Integr Comp Physiol 305:R187–R204. CrossRef Medline

Henry JP, Meehan WP, Stephens PM (1982) Role of subordination in nephritis of socially stressed mice. Contrib Nephrol 30:38–42. CrossRef Medline

Herman MA, Roberto M (2016) Cell-type-specific tonic GABA signaling in the rat central amygdala is selectively altered by acute and chronic ethanol. Addict Biol 21:72–86. CrossRef Medline

Herman MA, Cruz MT, Sahibzada N, Verbalis J, Gillis RA (2009) GABA signaling in the nucleus tractus solitarius sets the level of activity in dorsal motor nucleus of the vagus cholinergic neurons in the vagovagal circuit. Am J Physiol Gastrointest Liver Physiol 296:G101–G111. CrossRef Medline

Herman MA, Gillis RA, Vicini S, Dretchen KL, Sahibzada N (2012) Tonic GABAA receptor conductance in medial subnucleus of the tractus solitarius neurons is inhibited by activation of mu-opioid receptors. J Neurophysiol 107:1022–1031. CrossRef Medline

Herman MA, Contet C, Justice NJ, Vale W, Roberto M (2013) Novel subunit-specific tonic GABA currents and differential effects of ethanol in the central amygdala of CRF receptor-1 reporter mice. J Neurosci 33:3284–3298. CrossRef Medline

Herman MA, Contet C, Roberto M (2016) A functional switch in tonic GABA currents alters the output of central amygdala corticotropin releasing factor receptor-1 neurons following chronic ethanol exposure. J Neurosci 36:10729–10741. CrossRef Medline

Hida T, Shimizu N (1982) The interrelation between the laterodorsal tegmental area and lumbosacral segments of rats as studied by HRP method. Arch Histol Jpn 45:495–504. CrossRef Medline

Hou XH, Hyun M, Taranda J, Huang KW, Todd E, Feng D, Atwater E, Croney D, Zeidel ML, Osten P, Sabatini BL (2016) Central control circuit for context-dependent micturition. Cell 167:73–86.e12. CrossRef Medline

Huang CL, Wu MP, Ho CH, Wang JJ (2017) The bidirectional relationship between anxiety, depression, and lower urinary track symptoms: a nationwide population-based cohort study. J Psychosom Res 100:77–82. CrossRef Medline

Hurst JL, Beynon RJ (2004) Scent wars: the chemobiology of competitive signalling in mice. Bioessays 26:1288–1298. CrossRef Medline

Inoue T, Okusa MD (2015) Neuroimmune control of acute kidney injury and inflammation. Nephron 131:97–101. CrossRef Medline

Inoue T, Abe C, Sung SS, Moscalu S, Jankowski J, Huang L, Ye H, Rosin DL, Guyenet PG, Okusa MD (2016) Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through alpha7nAChR$^+$ splenocytes. J Clin Invest 126:1939–1952. CrossRef Medline

Janig W (2006) The integrative action of the autonomic nervous system. Cambridge, MA: Cambridge UP.

Kiddoo DA, Valentino RJ, Zderic S, Ganesh A, Leiser SC, Hale L, Grigoriadis DE (2006) Impact of the state of arousal and stress neuropeptides on urodynamic function in the freely moving rat. Am J Physiol Regul Integr Comp Physiol 290:R1697–R1706. CrossRef Medline

Kirby RS (2000) The natural history of benign prostatic hyperplasia: what have we learned in the last decade? Urology 56:3–6. CrossRef Medline

Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, Mehta AD, Levine YA, Faltys M, Zitnik R, Tracey KJ, Tak PP (2016) Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A 113:8284–8289. CrossRef Medline

Lechner SM, Curtis AL, Brons R, Valentino RJ (1997) Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. Brain Res 756:114–124. CrossRef Medline

Loewy AD, Saper CB, Baker RP (1979) Descending projections from the pontine micturition center. Brain Res 172:533–538. CrossRef Medline

Loewy AD, Franklin MF, Haxhiu MA (1994) CNS monoamine cell groups projecting to pancreatic vagal motor neurons: a transneuronal labeling study using pseudorabies virus. Brain Res 638:248–260. CrossRef Medline

Madden CJ, Stocker SD, Sved AF (2006) Attenuation of homeostatic responses to hypotension and glucoprivation after destruction of catecholaminergic rostral ventrolateral medulla (RVLM) neurons. Am J Physiol Regul Integr Comp Physiol 291:R751–R759. CrossRef Medline

Martelli D, Yao ST, McKinley MJ, McAllen RM (2014) Reflex control of inflammation by sympathetic nerves, not the vagus. J Physiol 592:1677–1686. CrossRef Medline

McDougall SJ, Guo H, Andresen MC (2017) Dedicated C-fibre viscerosensory pathways to central nucleus of the amygdala. J Physiol 595:901–917. CrossRef Medline

Noto H, Roppolo JR, Steers WD, de Groat WC (1989) Excitatory and inhibitory influences on bladder activity elicited by electrical stimulation in the pontine micturition center in the rat. Brain Res 492:99–115. CrossRef Medline

Page ME, Akaoka H, Aston-Jones G, Valentino RJ (1992) Bladder distention activates locus coeruleus neurons by an excitatory amino acid mechanism. Neuroscience 51:555–563. CrossRef Medline

Pavcovich LA, Valentino RJ (1995) Central regulation of micturition in the rat by corticotropin-releasing hormone from Barrington's nucleus. Neurosci Lett 196:185–188. CrossRef Medline

Pavlov VA, Tracey KJ (2017) Neural regulation of immunity: molecular mechanisms and clinical translation. Nat Neurosci 20:156–166. CrossRef Medline

Pitkänen A, Amaral DG (1994) The distribution of GABAergic cells, fibers, and terminals in the monkey amygdaloid complex: an immunohistochemical and in situ hybridization study. J Neurosci 14:2200–2224. Medline

Rickenbacher E, Baez MA, Hale L, Leiser SC, Zderic SA, Valentino RJ (2008) Impact of overactive bladder on the brain: central sequelae of a visceral pathology. Proc Natl Acad Sci U S A 105:10589–10594. CrossRef Medline

Roberto M, Madamba SG, Stouffer DG, Parsons LH, Siggins GR (2004) Increased GABA release in the central amygdala of ethanol-dependent rats. J Neurosci 24:10159–10166. CrossRef Medline

Roberto M, Cruz MT, Gilpin NW, Sabino V, Schweitzer P, Bajo M, Cottone P, Madamba SG, Stouffer DG, Zorrilla EP, Koob GF, Siggins GR, Parsons LH (2010) Corticotropin releasing factor-induced amygdala gamma-aminobutyric acid release plays a key role in alcohol dependence. Biol Psychiatry 67:831–839. CrossRef Medline

Saper CB (2002) The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neurosci 25:433–469. CrossRef Medline

Schiltz JC, Sawchenko PE (2007) Specificity and generality of the involvement of catecholaminergic afferents in hypothalamic responses to immune insults. J Comp Neurol 502:455–467. CrossRef Medline

Simerly RB, Swanson LW (1986) The organization of neural inputs to the medial preoptic nucleus of the rat. J Comp Neurol 246:312–342. CrossRef Medline

Simerly RB, Swanson LW (1988) Projections of the medial preoptic nucleus: a Phaseolus vulgaris leucoagglutinin anterograde tract-tracing study in the rat. J Comp Neurol 270:209–242. CrossRef Medline

Simerly RB, Gorski RA, Swanson LW (1986) Neurotransmitter specificity of cells and fibers in the medial preoptic nucleus: an immunohistochemical study in the rat. J Comp Neurol 246:343–363. CrossRef Medline

Singer AG, Beauchamp GK, Yamazaki K (1997) Volatile signals of the major histocompatibility complex in male mouse urine. Proc Natl Acad Sci U S A 94:2210–2214. CrossRef Medline

Stornetta RL, Inglis MA, Viar KE, Guyenet PG (2016) Afferent and efferent connections of C1 cells with spinal cord or hypothalamic projections in mice. Brain Struct Funct 221:4027–4044. CrossRef Medline

Svensson TH (1987) Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: putative implications for psychiatry and psychopharmacology. Psychopharmacology 92:1–7. CrossRef Medline

Swanson LW, Hartman BK (1976) The central adrenergic system: an immunofluorescence study of the location of cell bodies and their efferent connections in the rat using dopamine-*B*-hydroxylase as a marker. J Comp Neurol 163:467–505. CrossRef Medline

Thiele TE, Roitman MF, Bernstein IL (1996) c-Fos induction in rat brainstem in response to ethanol- and lithium chloride-induced conditioned taste aversions. Alcohol Clin Exp Res 20:1023–1028. CrossRef Medline

Travagli RA, Hermann GE, Browning KN, Rogers RC (2006) Brainstem

circuits regulating gastric function. Annu Rev Physiol 68:279–305. CrossRef Medline

Tucker DC, Saper CB, Ruggiero DA, Reis DJ (1987) Organization of central adrenergic pathways: I. Relationships of ventrolateral medullary projections to the hypothalamus and spinal cord. J Comp Neurol 259:591–603. CrossRef Medline

Ueno M, Ueno-Nakamura Y, Niehaus J, Popovich PG, Yoshida Y (2016) Silencing spinal interneurons inhibits immune suppressive autonomic reflexes caused by spinal cord injury. Nat Neurosci 19:784–787. CrossRef Medline

Valentino RJ, Page ME, Luppi PH, Zhu Y, Van Bockstaele E, Aston-Jones G (1994) Evidence for widespread afferents to Barrington's nucleus, a brainstem region rich in corticotropin-releasing hormone neurons. Neuroscience 62:125–143. CrossRef Medline

Valentino RJ, Chen S, Zhu Y, Aston-Jones G (1996) Evidence for divergent projections of corticotropin-releasing hormone neurons of Barrington's nucleus to the locus coeruleus and spinal cord. Brain Res 732:1–15. CrossRef Medline

Valentino RJ, Wood SK, Wein AJ, Zderic SA (2011) The bladder-brain connection: putative role of corticotropin-releasing factor. Nat Rev Urol 8:19–28. CrossRef Medline

Veinante P, Freund-Mercier MJ (1998) Intrinsic and extrinsic connections of the rat central extended amygdala: an in vivo electrophysiological study of the central amygdaloid nucleus. Brain Res 794:188–198. CrossRef Medline

Vincent SR, Satoh K (1984) Corticotropin-releasing factor (CRF) immunoreactivity in the dorsolateral pontine tegmentum: further studies on the micturition reflex system. Brain Res 308:387–391. CrossRef Medline

Wenker IC, Abe C, Viar KE, Stornetta DS, Stornetta RL, Guyenet PG (2017) Blood pressure regulation by the rostral ventrolateral medulla in conscious rats: effects of hypoxia, hypercapnia, baroreceptor denervation, and anesthesia. J Neurosci 37:4565–4583. CrossRef Medline

Willette RN, Morrison S, Sapru HN, Reis DJ (1988) Stimulation of opiate receptors in the dorsal pontine tegmentum inhibits reflex contraction of the urinary bladder. J Pharmacol Exp Ther 244:403–409. Medline

Wood SK, Baez MA, Bhatnagar S, Valentino RJ (2009) Social stress-induced bladder dysfunction: potential role of corticotropin-releasing factor. Am J Physiol Regul Integr Comp Physiol 296:R1671–R1678. CrossRef Medline

Yamaguchi M, Yamazaki K, Beauchamp GK, Bard J, Thomas L, Boyse EA (1981) Distinctive urinary odors governed by the major histocompatibility locus of the mouse. Proc Natl Acad Sci U S A 78:5817–5820. CrossRef Medline

Zhao Z, Wang L, Gao W, Hu F, Zhang J, Ren Y, Lin R, Feng Q, Cheng M, Ju D, Chi Q, Wang D, Song S, Luo M, Zhan C (2017) A central catecholaminergic circuit controls blood glucose levels during stress. Neuron 95:138–152.e5. CrossRef Medline