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Visceral Sensory Inputs to the Endocrine Hypothalamus

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Abstract

Interoceptive feedback signals from the body are transmitted to hypothalamic neurons that control pituitary hormone release. This review article describes the organization of central neural pathways that convey ascending visceral sensory signals to endocrine neurons in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus in rats. A special emphasis is placed on viscerosensory inputs to corticotropin releasing factor (CRF)-containing PVN neurons that drive the hypothalamic-pituitary-adrenal axis, and on inputs to magnocellular PVN and SON neurons that release vasopressin (AVP) or oxytocin (OT) from the posterior pituitary. The postnatal development of these ascending pathways also is considered.

Introduction

Interoceptive feedback signals from the body are conveyed to widely distributed regions of the central nervous system (CNS), including regions of the hypothalamus and limbic forebrain that initiate and modulate autonomic and endocrine homeostatic processes. This review article describes the organization of central neural pathways that transmit sensory signals from thoracic and abdominal viscera to endocrine neurons in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. A special emphasis is placed on viscerosensory inputs to parvocellular corticotropin releasing factor (CRF)-containing PVN neurons that control anterior pituitary release of adrenocorticotropic hormone (ACTH), and on inputs to magnocellular PVN and SON neurons that release vasopressin (AVP) or oxytocin (OT) from their axon terminals in the posterior pituitary. The postnatal development of these ascending pathways also is considered. In laboratory rats, central visceral sensory pathways undergo a significant amount of synaptic assembly and refinement during the first two weeks of postnatal life. The anatomical and functional maturation of interoceptive inputs to the endocrine hypothalamus appears to parallel the organism's newly emerging ability to respond physiologically to certain environmental challenges.

Visceral sensory inputs to spinal cord and caudal brainstem

Sensory signals from the viscera are carried to the CNS by spinal and cranial afferents. In rats, spinal viscerosensory afferents terminate in laminae I–VII of the dorsal horn and intermediate zone, and in lamina X around the central canal [1]. Inputs from visceral and somatic sensory afferents converge onto common second order neurons within the spinal dorsal horn. A subset of these neurons convey the convergent somato- and viscerosensory signals to the diencephalon via the anterolateral spinothalamic tract. A separate spinal viscerosensory pathway relays through lamina X, medial lamina VII, and the dorsal gray commissure to ascend at the junction

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of the gracile and cuneate fasciculi [2;3]. This viscerotopically organized pathway provides direct and relayed inputs to the medullary nucleus of the solitary tract (NST), ventrolateral medulla (VLM), pontine parabrachial nucleus (PBN), and hypothalamus [2;3;4;5;6;7;8]. Although spinal inputs to the hypothalamus do not appear to directly target endocrine neurons, they synapse within regions of the lateral hypothalamus that do [9].

In addition to relayed spinal sensory inputs, the NST receives direct sensory inputs from thoracic and abdominal viscera via glossopharyngeal and vagal cranial afferents. Glossopharyngeal and vagal sensory neurons innervate the heart and associated cardiovascular targets [10], and vagal sensory neurons innervate the gut and associated digestive viscera from the oral cavity through the colon [11;12;13]. Central glossopharyngeal and vagal afferent fibers enter the dorsolateral medulla via multiple sensory rootlets and converge within the solitary tract, analogous to the spinal trigeminal tract or Lissauer's tract, which conveys the viscerosensory axons along the rostrocaudal length of the NST [11].

Central visceral sensory pathways to the endocrine hypothalamus

As summarized in Figure 1, visceral sensory signals are relayed from the NST to the endocrine hypothalamus via direct and indirect ascending pathways [14;15;16;17]. The indirect pathways include relays from the area postrema (AP) and NST to the VLM [16;18;19;20] and PBN [21;22;23;24]. The AP is a circumventricular organ with a reduced or absent blood-brain barrier. Projections from AP neurons to the subjacent NST and also directly to the VLM and PBN [22;23;25] provide a neural route for blood-borne signals (e.g., cytokines, osmolytes, hormones, toxins) to affect central viscerosensory processing.

The NST, VLM and PBN each contain neurons that project directly to the hypothalamus [14; 16;26;27;28], although PBN inputs to the PVN and SON are relatively sparse. PVN and SON endocrine neurons receive direct synaptic input from the NST and VLM, but receive little or no direct input from the PBN [28;29;30]. The PBN instead provides robust inputs to the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST) [28;31;32], both of which also receive direct inputs from the NST and VLM. The CeA and BNST are highly interconnected [33], and the ventrolateral BNST densely innervates the medial parvocellular PVN (PVNmp) [34;35]. Caudal VLM neurons that receive indirect input from arterial baroreceptors and from the cervical vagus nerve (via the NST) have long ascending axons that terminate directly on neurohypophyseal and tuberoinfundibular PVN neurons [30].

Viscerosensory recruitment of neural inputs to the endocrine hypothalamus

The ability of visceral sensory stimuli to affect pituitary hormone release has been appreciated for many years. Early studies demonstrated posterior pituitary release of antidiuretic and milk-ejection factors (i.e., AVP and OT, respectively) in rats after electrical stimulation of the central end of the cut vagus nerve [36;37;38;39;40]. A series of studies by Ueta and colleagues subsequently demonstrated that gastrointestinal and vagal stimulation promotes significant activation of magnocellular and parvocellular endocrine neurons within the PVN and SON in anesthetized rats [41;42;43]. Some of these experiments involved mechanical gastric distension or electrical stimulation of vagal afferents, while others involved pharmacological stimulation of gastrointestinal vagal afferents via systemic administration of cholecystokinin octapeptide (CCK).

Exogenously administered CCK provides a useful experimental tool with which to activate ascending visceral sensory pathways. Systemic CCK increases pituitary hormone release via CCK-1 receptor-mediated activation of vagal afferent inputs to the caudal medulla that recruit central ascending viscerosensory pathways to the hypothalamus [43;44;45;46;47;48]. In 1986 it was reported that synthetic CCK administered peripherally at supraphysiological doses

potently stimulates pituitary OT (but not AVP) secretion in rats [49]. The OT secretory responses to CCK administration were markedly attenuated after bilateral subdiaphragmatic vagotomy, after capsaicin-induced sensory vagotomy, or after systemic blockade of CCK-1 receptors [49;50]. In rats, systemic CCK increases the firing rate of magnocellular OT neurons, and transiently inhibits the firing of magnocellular AVP neurons [51]. Plasma OT levels also are increased by gastric distension, which synergizes with exogenous CCK to further elevate plasma OT in rats [49]. In addition to increasing plasma OT levels, systemic CCK administration alters pituitary release of growth hormone and thyrotropin in adult male rats [52;53;54]. Interestingly, systemic CCK increases plasma levels of AVP but not OT in humans [55] and ferrets [56], and increases plasma levels of AVP, luteinizing hormone, gonadotropin-releasing hormone, and ACTH in rhesus macaques [57;58;59]. It is unclear why rats and mice release OT after CCK administration, whereas ferrets, primates, and rabbits (Dr. Loretta Flanagan-Cato, personal communication) release AVP instead. Although the reason for the species difference is unclear, the pattern of hormone release is consistent with known species differences in endocrine responses to stress. The doses of synthetic CCK used to stimulate endocrine secretion are nauseogenic and even emetic in humans, and promote sickness-like behavior and HPA axis activation in rats and other experimental animals. Rats and mice release OT along with ACTH during stress responses, whereas humans and non-human primates release ACTH and AVP.

The natural ligand for endogenous CCK-1 receptors is CCK that is released from the gut in a nutrient-dependent manner. Circulating plasma levels of endogenous CCK increase transiently in rats and other mammals (including humans) after food intake, representing peptide “spillover” into the systemic circulation after CCK is released locally near its sites of action within digestive tissues and along gastrointestinal vagal afferent fibers. Under normal circumstances, endogenous CCK acts at its receptors to initiate and maintain various digestive processes, and also to promote satiety. Although a very large or calorically dense meal might produce homeostatic stress, it is unlikely that endogenous CCK released after a typical meal activates the same ascending visceral pathways as are activated by synthetic CCK, and normal meal-related satiety may have nothing to do with the ability of CCK or gastric distension to stimulate hypothalamic endocrine neurons. Indeed, the ability of CCK to promote satiety seems to require only neural circuits that are contained within the caudal brainstem [47;60;61]. Thus, it remains unclear whether either endogenously released CCK or natural meal-related gastric distension contributes to recruitment of hypothalamic endocrine neurons. As discussed further, below, it has been shown that voluntary intake of a large meal by rats activates only a subset of the NST visceral sensory neurons that are activated after systemic CCK or other “interoceptive stress” treatments [62]. Nevertheless, the ability of synthetic CCK, mechanical gastric distension, and vagal nerve stimulation to alter pituitary hormone secretion provides compelling evidence for the sufficiency of visceral sensory pathways to recruit the endocrine hypothalamus.

Viscerosensory inputs to the endocrine hypothalamus are primarily noradrenergic

Viscerosensory projections from the NST and VLM to the PBN, hypothalamus, CeA, and BNST are primarily (although not exclusively) catecholaminergic, arising from nor/adrenergic A2/C2 neurons within the NST and A1/C1 neurons within the VLM [19;26;63]. For convenience, in this article catecholaminergic NST and VLM projection neurons are referred to collectively as noradrenergic (NA) neurons, because they all are immunoreactive for the NA synthetic enzyme dopamine beta hydroxylase (DbH). Various peptides are co-expressed by these NA neurons, including those that project directly to the PVN and SON [48;64;65;66].

Dense NA inputs to the PVN (Figure 2) and SON arise almost exclusively from the NST and VLM, with an additional restricted input to the periventricular PVN that arises from the pontine locus coeruleus [19;26;67]. The PVN and SON contain high densities of adrenergic receptors in subregions that receive input from the NST and VLM [19;67;68]. Ascending NA projections from the NST and VLM course primarily through the ventral noradrenergic ascending bundle (VNAB) (Figure 1) [19;67]. Electrical stimulation of the VNAB elicits CRF secretion through an adrenergic receptor-mediated mechanism [69], and increases plasma levels of ACTH. Similarly, direct stimulation of the NST and VLM increases PVN neuronal firing and pituitary secretion [70;71], and these effects are attenuated by prior destruction of NA terminals within the PVN [70].

Peripheral visceral stimuli also recruit activation of medullary NA neurons that project to the hypothalamus and limbic forebrain, coincident with increased NA release at target sites. For example, extracellular NA content increases in the PVN after systemic administration of CCK, which, as reviewed above, activates vagal sensory inputs to the NST and stimulates pituitary release of several hormones. Systemic CCK activates NA neurons within the NST and VLM in rats [48], ferrets [56], and rhesus macaques [72]. In rats, NA neurons activated after CCK administration include those that project directly to the PVN [46], and immunotoxin-induced destruction of these NA neurons attenuates the ability of systemic CCK to activate Fos expression within PVN endocrine neurons [27]. A CCK-induced increase in NA content measured within the PVN directly parallels increased plasma levels of ACTH and OT in rats, consistent with the predominantly excitatory effects of systemic CCK and synaptic effects of NA on hypothalamic CRF and OT neurons [73;74;75;76]. Voluntary food intake also promotes NA neural activation within the NST and VLM in rats, and the proportion of NA neurons activated in both regions increases in proportion with the size of the meal consumed [77]. However, it is unclear whether food intake and exogenous CCK activate the same medullary NA neurons, including those that project to the hypothalamus.

Within the PVN neuropil, NA terminals have been reported to form both symmetric- and asymmetric-type synapses with the dendrites and somata of presumptive endocrine neurons, including ones immunoreactive for OT, AVP, CRF, and thyrotropin releasing hormone [78; 79;80;81;82;83;84;85;86;87;88;89]. Magnocellular subregions of the PVN that control AVP and OT release from the posterior pituitary appear to be preferentially targeted by NA inputs arising in the VLM, whereas NA projections arising in the NST appear to preferentially target magnocellular OT neurons within the PVN and SON [90], and CRF neurons within the PVNmp [30;91]. CRF neurons summate excitatory and inhibitory inputs into a net secretory signal to drive ACTH release from anterior pituitary corticotrophs [92;93]. Thus, CRF neurons within the PVNmp control basal, circadian, and stress-induced glucocorticoid secretion via the HPA axis [94;95;96;97]. Ample evidence indicates that NA inputs provide critical control over the activity of these stress-responsive CRF neurons [95;98;99;100;101].

Recent findings indicate that NA inputs to the PVNmp are provided by NST and/or VLM neurons with collateralized inputs to the BNST [102]. Immunotoxic lesioning methods have demonstrated that these NA inputs are necessary for systemic yohimbine (a sympathomimetic adrenergic signal-enhancing drug) to activate neural expression of the immediate-early gene product, Fos, in CRF neurons within the PVNmp, and to increase plasma corticosterone levels [102]. Similar preliminary results have been obtained in toxin-lesioned rats subsequently treated with systemic lithium chloride (LiCl) (Figure 2). Conversely, inputs to magnocellular regions of the PVN and SON appear to arise from medullary NA neurons that do not also project to either the BNST or the PVNmp [102]. This finding complements previous evidence that magnocellular and parvocellular PVN subdivisions are differentially innervated by NA inputs arising from the VLM and NST, respectively [91]. In addition to its direct NA input, the PVNmp receives a dense projection from neurons within the same BNST region [35] that

is heavily innervated by medullary NA neurons [103;104]. Thus, NA-mediated viscerosensory modulation of neural function within the endocrine PVN includes direct inputs from medullary NA neurons, and indirect inputs that are relayed through the BNST.

Non-catecholaminergic viscerosensory inputs to the hypothalamus

Ascending NA projections to the hypothalamus and limbic forebrain are paralleled by projections arising from a separate and smaller population of non-NA neurons with widely arborizing axon terminals, whose cell bodies are located in the caudal NST and adjacent reticular formation. These neurons appear to coexpress immunoreactivity for multiple peptides, including glucagon-like peptide 1 (GLP-1) [63;90;105;106;107;108]. The synaptic targets of GLP-1 neurons include CRF neurons in the PVNmp [109] and OT neurons in the magnocellular PVN and SON (Figure 3), where GLP-1 binding sites and receptor gene expression are localized [110;111;112;113;114]. Cells in the caudal NST and adjacent reticular formation provide the sole source of endogenous ligand for these GLP-1 receptors [90;106], and ascending GLP-1 fiber projections appear to follow the VNAB, intermingled with NA fibers (Figure 1).

Central infusions of GLP-1 or GLP-1 receptor agonists activate PVN neurons (Figure 3) and increase plasma levels of ACTH and OT [115;116;117;118;119;120;121;122]. Several different interoceptive stressors (e.g., systemic CCK, LiCl, lipopolysaccharide) activate Fos expression by medullary GLP-1 neurons, including those that project to the PVN [62]. Other studies have demonstrated that central GLP-1 receptor signaling pathways contribute to the ability of these stressors to recruit the HPA axis [121;123;124]. Thus, “stressful” viscerosensory stimuli appear to recruit ascending GLP-1-containing neural pathways in a manner similar to the recruitment of ascending NA pathways. Interestingly, although medullary NA neurons are activated in rats after food intake [77], voluntary ingestion of even a very large meal does not activate GLP-1 neurons [62]. Mechanical gastric distension can activate Fos expression in GLP-1 neurons [125], evidence that they do respond to gastric sensory input if stimulation is robust enough. Recruitment of hindbrain GLP-1 neurons, including those that innervate the hypothalamus, may depend on the intensity or modality of visceral stimulation, and may even differentiate stressful from non-stressful visceral stimuli [62].

Postnatal development of viscerosensory inputs to the endocrine hypothalamus

The natural process of neural circuit development offers special opportunities to probe the functional organization of ascending viscerosensory pathways. Developmental research in this area has been fairly limited, but the results are intriguing. The first few postnatal weeks in rats correspond to a so-called “stress hyporesponsive period” (SHRP) characterized by reduced or absent HPA axis responsiveness to certain types of stressors [126;127;128], including interoceptive stressors [47;129;130]. The causal factors underlying the SHRP remain controversial, and are likely to be multiple and complex [129;131;132;133]. It appears that the SHRP is not simply due to an inability of hypothalamic, anterior pituitary, and/or adrenal components of the HPA axis to respond to input, because certain stimuli can increase hypothalamic Fos expression, activate the HPA axis, and increase plasma levels of ACTH, cortisol, OT and AVP in rat pups during the SHRP [128;129;134]. We have proposed that the SHRP is at least partially due to structural and/or functional immaturity of ascending NA (and perhaps GLP-1-containing) neural pathways that carry visceral sensory inputs from the caudal medulla to the PVN.

Early catecholamine histofluorescence studies suggested that NA inputs to the hypothalamus and limbic forebrain are essentially absent in rats at birth [135;136]. More sensitive

immunocytochemical techniques and tract-tracing later demonstrated that NA projections from the NST and VLM to the PVN actually are already present in newborn rats [130]. However, the density of NA terminals in the PVN increases markedly during the first three weeks of postnatal development [130], in concert with increasing levels of hypothalamic NA [137; 138]. Additional evidence for delayed maturation of ascending NA inputs is offered by analysis of fiber immunolabeling for prolactin releasing peptide (PrRP), which is co-expressed by a subset of NA neurons within the NST [66;139]. The NST is the only source of PrRP-positive fibers within the CNS; thus, immunohistochemical detection of PrRP-positive fibers provides a useful and discrete marker for ascending NST projections during development. PrRP-positive fibers are first visible within the ventral lateral BNST on postnatal day (P) 3 [140]. By P6, PrRP fibers are present within the PVN and other forebrain targets, although their density is not as great at this early time point as in adult rats [140].

The apparent structural immaturity of ascending NA inputs to the PVN in neonatal rats predicts that neurons within the developing hypothalamus are less sensitive to viscerosensory signals in neonatal vs. adult rats. Indeed, although systemic CCK activates neurons within the caudal brainstem [47] and suppresses independent ingestion in neonatal rats [141;142;143], CCK does not activate Fos expression in the hypothalamus or other forebrain regions, and does not stimulate pituitary hormone release in neonatal rats [47]. The ability of exogenous CCK to engage medullary NST neurons and to suppress food intake in 2-day-old rats means that CCK-1 receptor-mediated activation of vagal afferent inputs to the NST and subsequent processes for recruitment of brainstem circuits that underlie CCK-induced hypophagia already are functional. This is not surprising, because anatomical tracing studies revealed a precocious development of vagal viscerosensory inputs to the NST during embryonic development [144]. In newborn rat pups, exogenous CCK causes a significant increase in the excitability of NST neurons that are synaptically activated by electrical stimulation of the subdiaphragmatic vagus nerve, and the increased sensitivity is blocked by a specific CCK-1 receptor antagonist [145]. A similar pattern of NST activation occurs in neonatal rats after more naturalistic feeding-induced vagal stimulation [146], although that study did not investigate hypothalamic activation after feeding in neonates.

The hindbrain distribution of neural Fos expression is virtually identical in 2-day-old and adult rats after CCK treatment, with activated neurons located in specific subregions of the NST that receive gastric vagal sensory input [47]. Conversely, the lack of hypothalamic activation in neonatal rats after CCK treatment is consistent with other evidence for delayed postnatal maturation of ascending NA projections from the NST and VLM [147] that transmit viscerosensory information from hindbrain to hypothalamus in adult rats [19;26;46;148]. Another recent study investigated the postnatal maturation of central neural Fos responses to LiCl, a malaise-inducing agent [149]. Rat pups were injected i.p. with 0.15M LiCl (2% BW) or control solution (0.15M NaCl) at multiple time points between the day of birth (P0) and P28. Compared to Fos activation after control saline treatment, LiCl did not increase Fos in the PVN or other forebrain regions on P0, but did so on P7 and later. Maximal PVN Fos responses to LiCl were observed on P14, whereas LiCl-induced BNST activation continued to increase through P28. Comparable results have been obtained by others examining central Fos responses to an acute lipopolysaccharide challenge in developing rats [150]. These findings provide additional evidence that central interoceptive circuits in rats are not fully functional at birth, but instead show age-dependent increases in neural recruitment following viscerosensory stimulation.

Given the apparent inability of systemic CCK, LiCl, or lipopolysaccharide to activate hypothalamic neurons in neonatal rats, one might hypothesize that the endocrine hypothalamus is refractory to all excitatory inputs early in development. This turns out not to be the case. For example, acute osmotic dehydration robustly activates hypothalamic Fos expression and

increases pituitary hormone levels in neonatal rats [134]. The important difference seems to be the ability of osmotic dehydration to activate PVN and SON neurons without requiring ascending viscerosensory inputs from the caudal brainstem [151]. Thus, the lack of neonatal hypothalamic responsiveness to CCK, LiCl, and other visceral sensory stimuli is most likely due to functional immaturity of ascending viscerosensory inputs from the NST and VLM to the hypothalamus.

Conclusion

Visceral sensory information reaches the endocrine hypothalamus via central neural pathways that are primarily, but not exclusively, noradrenergic. NA and complementary peptidergic (e.g., GLP-1) inputs to magnocellular and parvocellular endocrine neurons within the SON and PVN arise directly from medullary NST and VLM neurons, with additional viscerosensory inputs relayed through the pontine PBN and other central sites. The functional importance of these pathways for modulating and driving HPA axis and other endocrine responses to interoceptive stimuli has been demonstrated by experiments involving pathway lesioning and pharmacological blockade in adult rats, and through the natural process of neural development in neonatal rats.

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Abbreviations

ACTH
adrenocorticotropic hormone

AP
area postrema

AVP
arginine vasopressin

BNST
bed nucleus of the stria terminalis

CeA
central nucleus of the amygdale

CCK
cholecystokinin octapeptide

CNS
central nervous system

CRF
corticotropin-releasing factor (hormone)

DbH
dopamine beta hydroxylase

GLP-1
glucagon-like peptide 1

LiCl
lithium chloride

NA
noradrenergic

NST
nucleus of the solitary tract

OT
oxytocin

P
: postnatal day

PBN
: parabrachial nucleus

PrRP
: prolactin releasing peptide

PVN
: paraventricular nucleus of the hypothalamus

PVNlm
: lateral magnocellular PVN

PVNmp
: medial parvocellular PVN

SHRP
: stress hyporesponsive period

SON
: supraoptic nucleus of the hypothalamus

VLM
: ventrolateral medulla

VNAB
: ventral noradrenergic ascending bundle

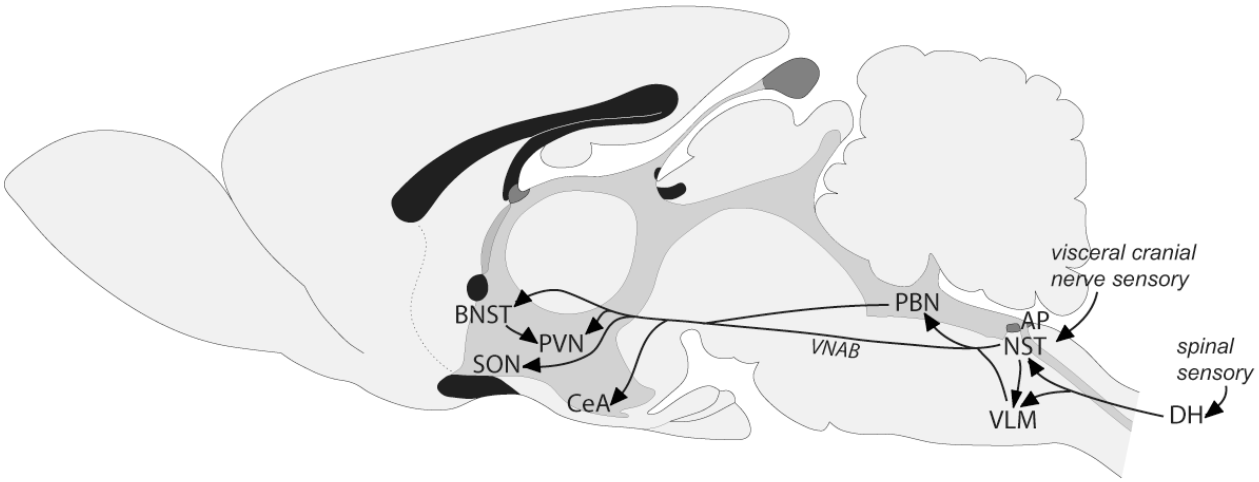

Figure 1.
Schematic of ascending pathways (arrows) through which visceral sensory signals from the spinal cord and caudal brainstem reach the hypothalamus and limbic forebrain. Multiple interconnections among these brain regions are not shown, including reciprocal connections between the CeA and BNST, and descending projections from the hypothalamus and limbic forebrain to the PBN, NST and VLM. *See abbreviation list.*

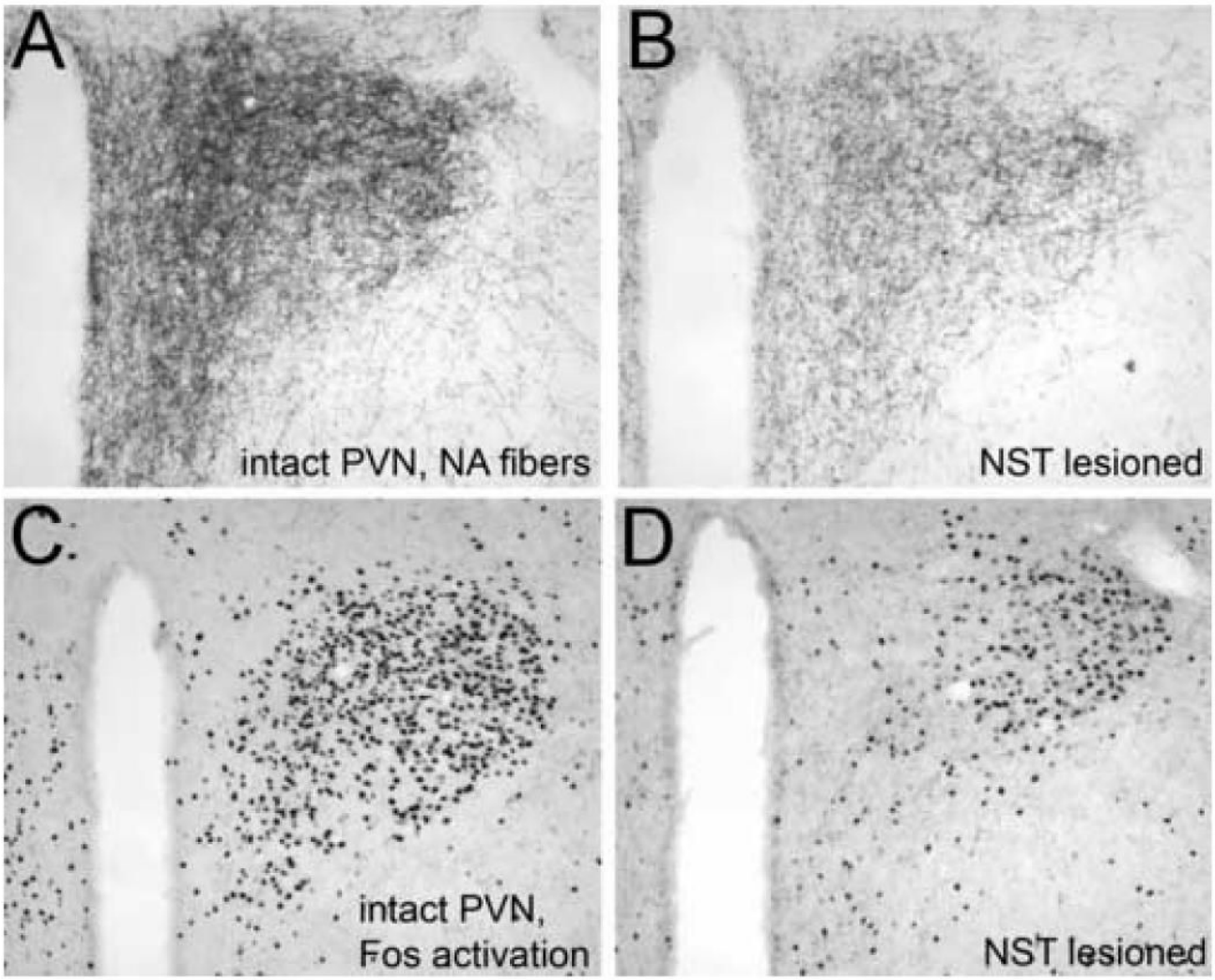

Figure 2.

Immunoperoxidase labeling of DbH-positive NA fibers within the PVN in an intact adult rat (A) and in a rat following toxin-induced destruction of NA neurons within the NST (B). Systemic administration of LiCl (0.15M, 2% BW, i.p.) induces robust neural Fos expression within the medial parvocellular and lateral magnocelluar PVN of the intact rat (C), but attenuated Fos expression within the medial parvocellular PVN of the toxin-lesioned rat (D). Remaining NA fibers presumably arise from the VLM and from residual non-lesioned NST neurons, although the LC may contribute NA inputs to the periventricular region. *See abbreviation list.*

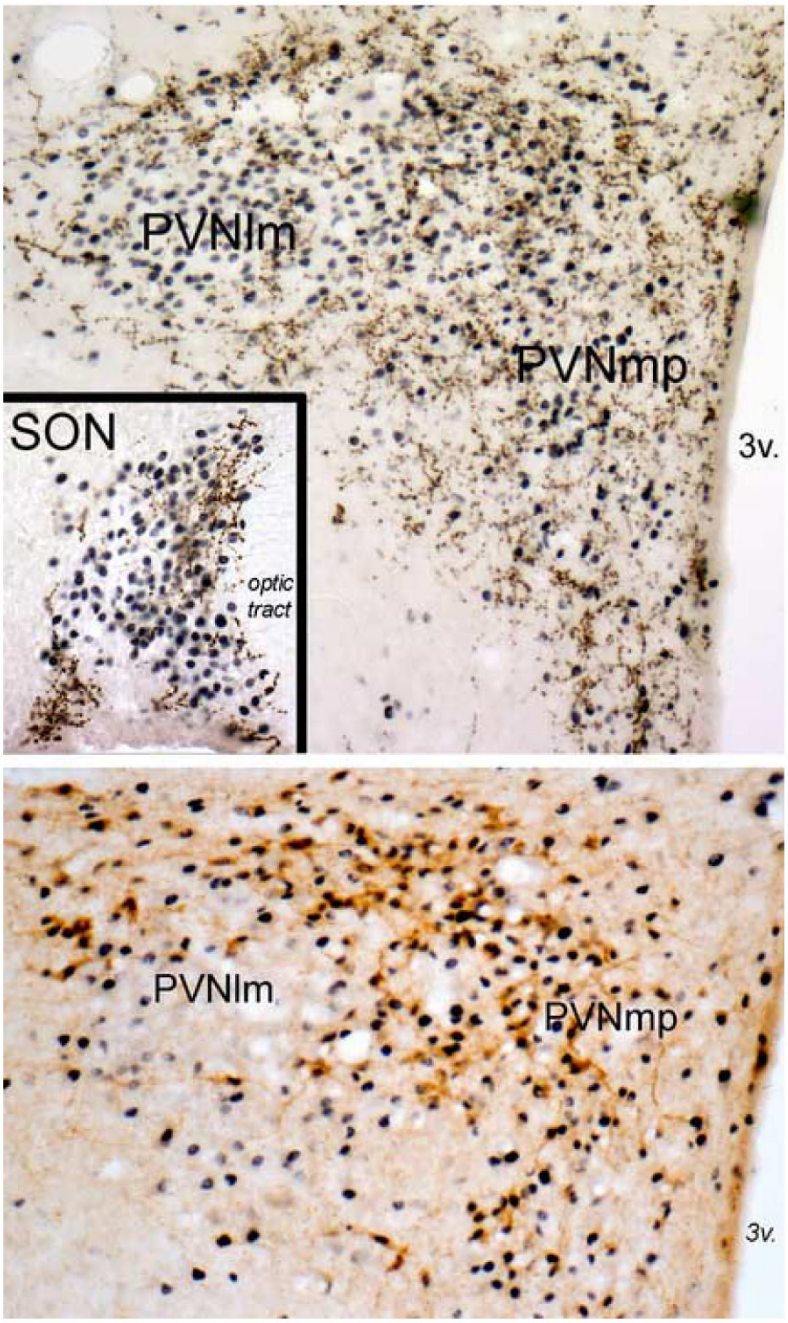

Figure 3.

The top panel and inset depict immunoperoxidase labeling of GLP-1 immunopositive fibers (brown) within the PVN and SON (inset) in an adult rat after systemic administration of LiCl (0.15M, 2% BW, i.p.). Robust LiCl-induced neural Fos expression (blue-black nuclear label) is present throughout the PVN, including the PVNmp and PVNlm. GLP-1-positive fibers are largely absent within the core of the PVNlm, where AVP-positive neurons cluster in rats. Instead, GLP-1-positive fibers are distributed around the perimeter of the PVNlm, where magnocellular OT neurons predominate, and throughout the PVNmp, where parvocellular CRF and OT neurons predominate. LiCl-induced Fos expression also is prevalent throughout the SON (inset), where GLP-1-positive fibers cluster within the dorsal and medial SON where

magnocellular OT neurons predominate. The lower panel depicts immunoperoxidase labeling of CRF-positive neurons (brown) within the PVN in an adult rat perfused 90 min after intracerebroventricular infusion of 1.0 g of synthetic GLP-1-(7–36) amide. Fos expression is robust within the PVNmp, including activation of the majority of CRF-positive neurons. Conversely, Fos is largely absent within the core of the PVNlm, where magnocellular AVP neurons predominate. 3v, third ventricle. *See abbreviation list.*