from 0 to 28 μA. Ascending and descending series of intensities were counterbalanced over 2 days, providing separate ascending and descending rate-intensity functions for each animal. In both series the experimenter delivered three primes at each current intensity; the subsequent rate of ICS was determined over 5 minutes.
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Central Noradrenergic Pathways for the Integration of Hypothalamic Neuroendocrine and Autonomic Responses

Abstract. *Immunohistochemical and axonal transport methods were used to describe the organization of a series of central noradrenergic pathways that interrelate the nucleus of the solitary tract, which receives primary visceral sensory information, and the paraventricular and supraoptic nuclei of the hypothalamus, which participate in autonomic and neuroendocrine modes of homeostatic control. The results indicate that pathways arising from noradrenergic cells in the dorsal vagal complex, the ventrolateral medulla, and the locus coeruleus end in specific subdivisions of the paraventricular and supraoptic nuclei which are involved in the regulation of responses from the pituitary gland and from both divisions of the autonomic nervous system. This circuitry may play an important role in the integration of hypothalamic responses to visceral stimuli.*

The maintenance of a stable internal milieu requires precise coordination of autonomic and endocrine responses to particular visceral stimuli. One approach to understanding the central mechanisms that mediate this coordination involves the elucidation of neural pathways that interrelate the nucleus of the solitary tract (NST), which is the principal recipient of primary visceral afferent information carried by the vagus (X) and glossopharyngeal (IX) nerves, with the hypothalamus, which plays an important role in the expression of neuroendocrine and autonomic responses. Since the paraventricular nucleus (PVN) of the hypothalamus appears to be involved in both modes of hypothalamic control (*1*), it may be useful for the study of neural mechanisms that underlie integrated visceral responses.

The magnocellular division of the PVN and the supraoptic nucleus (SON) play a role in synthesizing vasopressin and oxytocin and in controlling their release from the posterior lobe of the pituitary gland (*2*). Essentially separate and topographically distinct populations of cells in the parvicellular division of the PVN project to preganglionic cell groups of both divisions of the autonomic nervous system and to the median eminence, affording the nucleus a measure of control over anterior pituitary function as well (*3*). Because the PVN contains both functionally and anatomically distinct cell groups, neuroendocrine and autonomic responses may be integrated by way of afferent pathways that differentially innervate various subpopulations of neurons in the nucleus (*1*).

The experiments reported here clarify the organization of pathways that interrelate the NST and the PVN and SON in the rat. The NST projects directly to the PVN (*4*) through a pathway that is at least partially noradrenergic (*5*). However, this projection appears to innervate primarily the parvicellular division of the

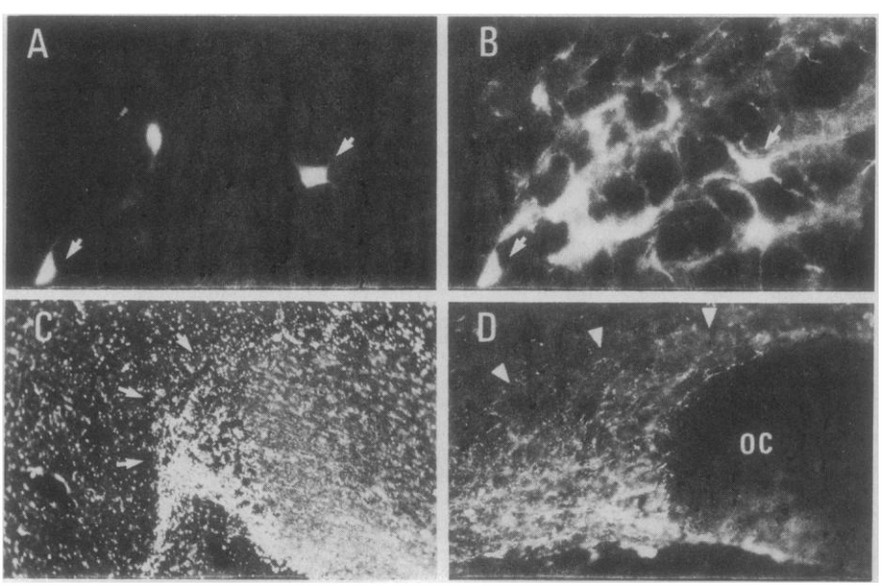

Fig. 1. (A and B) High-power fluorescence photomicrographs of the same field in the ventrolateral medulla, taken with different excitation wavelengths. (A) Cells retrogradely labeled after an injection of True Blue into the PVN. (B) A cluster of dopamine-β-hydroxylase–stained cells in the A1 catecholaminergic cell group. Two cells (arrowheads) clearly contain both dyes and are, therefore, dopamine-β-hydroxylase–containing neurons that project to the region of the PVN (× 250). (C and D) Photomicrographs showing (C) the distribution of anterogradely transported tritiated amino acids in the SON after an injection in the A1 region of the ventrolateral medulla and (D) the distribution of dopamine-β-hydroxylase–stained fibers in the SON of a normal rat brain. The injection was centered in the region of retrogradely labeled cells shown in (A). Note that the labeled terminal field in (C) and the noradrenergic fibers in (D) are both concentrated in the ventral part of the nucleus (arrowheads indicate nuclear borders) which contains predominantly vasopressinergic neurons (× 70). Abbreviation: *oc*, optic chiasm (lateral border).

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nucleus (*4*). In view of physiological (*6*) and anatomical (*7*) evidence that activation of particular classes of visceral afferents can influence vasopression secretion through noradrenergic mechanisms, we reasoned that additional noradrenergic pathways may relay information from the NST to the magnocellular division of the PVN and SON.

To identify noradrenergic cell groups that may project to these nuclei, we used a new method (*8*) that allows simultaneous localization of an antigen and a retrogradely transported marker, the fluorescent dye True Blue. After small (20 to 30 nl) injections of the tracer were stereotaxically placed in the PVN ($N = 4$), a number of retrogradely labeled cell groups were observed in the brainstem. In three distinct regions, over 80 percent of the labeled cells also cross-reacted with an antiserum to dopamine-β-hydroxylase, a specific marker for noradrenergic and adrenergic neurons. The regions that contained a vast majority of the doubly labeled neurons were the locus coeruleus, the A2 catecholamine cell group (*9*) centered in the dorsal vagal complex, and the A1 catecholamine group in the ventrolateral medulla (Fig. 1, A and B, and Fig. 2A), which lies just dorsal to the lateral reticular nucleus (*10*). Cell counts showed that 68 percent of the retrogradely labeled neurons in these three areas were in the ventral medullary (A1) group, 26 percent were in the dorsal vagal (A2) group, and 6 percent were in the locus coeruleus. In addition, each of the projections was at least partially crossed, and no other dopamine-β-hydroxylase–stained cell groups contained more than a few doubly labeled cells. Injections of True Blue centered in, but not restricted to, the SON ($N = 2$) yielded a similar pattern of double labeling, although the total number of such cells was only 36 percent of that seen following injections into the PVN. Of these, 74 percent were in the ventral medullary (A1) group, 15 percent were in the dorsal vagal (A2) group, and 11 percent were in the locus coeruleus.

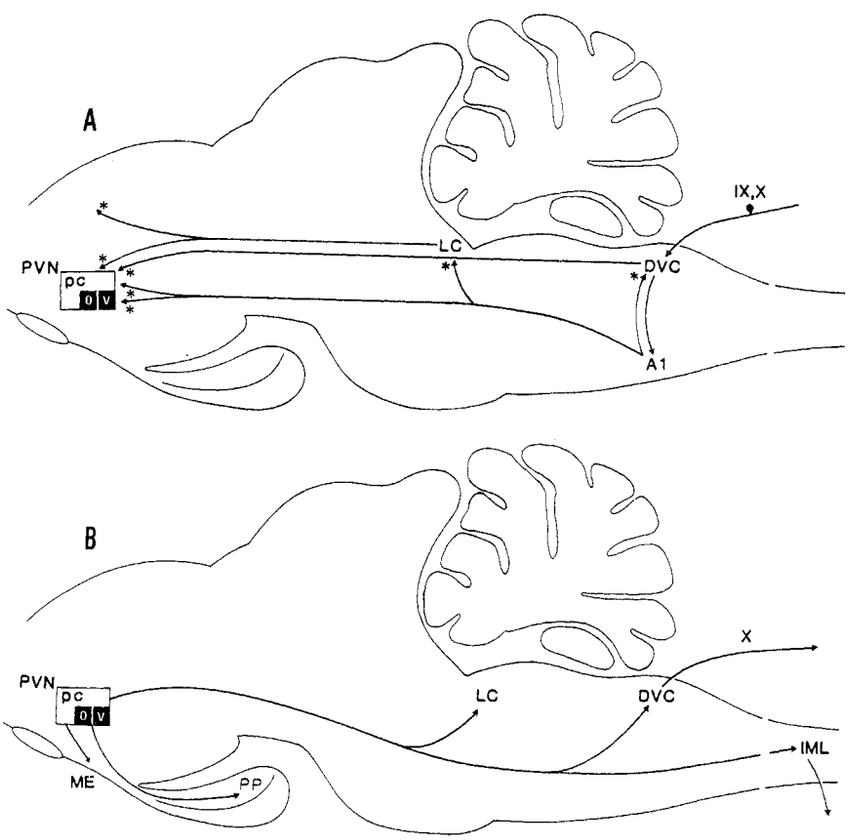

Fig. 2. (A) Organization of ascending, predominantly noradrenergic projections (asterisks) to the PVN; the SON has been omitted for clarity. Note the interconnections between the three noradrenergic cell groups that project to the PVN and the fact that only the A1 group substantially innervates both the magnocellular and parvicellular divisions of the PVN. (B) Organization of efferent projections from the PVN which appear to be involved in the central control of cardiovascular function. The parvicellular division projects to preganglionic cell groups of both divisions of the autonomic nervous system in the brainstem and the spinal cord; to the locus coeruleus, a nucleus that appears to influence the intracerebral microvasculature; and to the median eminence. Neurons in the magnocellular division of the PVN (and the SON) project directly to the posterior lobe of the pituitary gland, where they release vasopressin into the general circulation. Abbreviations: *A1*, A1 catecholaminergic cell group; *DVC*, dorsal vagal complex; *ME*, median eminence; *IML*, intermediolateral cell column of spinal cord; *IX*, glossopharyngeal nerve; *X*, vagus nerve; *LC*, locus coeruleus; *PP*, posterior pituitary; *pc*, parvicellular division of the PVN; *O* and *V*, oxytocin- and vasopressin-containing portions of the magnocellular division of the PVN.

To establish the precise distribution of fibers in PVN and SON which arise from the locus coeruleus, the A1 group, and the A2 group, we took advantage of the observation that the projection from each of these regions appears to be primarily noradrenergic. Small injections (30 nl) of a mixture of [^{3}H]proline and [^{3}H]leucine (50 μCi/μl) were placed into one or another of the groups in different animals (*11*). The pattern of silver grains in autoradiographs of the PVN and SON was taken to represent the distribution of noradrenergic terminals from the injected cell group.

We confirmed (*12*) that such injections, centered in the locus coeruleus ($N = 3$), label only medial parts of the PVN; silver grains were confined primarily to the periventricular part of the parvicellular division (*1, 3, 7*) and did not exceed background levels in the SON. Injections centered in the dorsal vagal complex at the level of the obex (A2 group) ($N = 10$) labeled a substantial projection to the periventricular, medial, and dorsal parts of the parvicellular division of the PVN; again, no clear labeling was found in the magnocellular division of the PVN (*4*) or in the SON (*13*). In contrast, injections centered in the ventral medullary (A1) group ($N = 7$) labeled a relatively massive input to those portions of the magnocellular divisions of the PVN and SON in which vasopressin-containing cells are concentrated (Fig. 1, C and D). The injections also labeled a dense input to the parvicellular part of the PVN, a projection which overlaps that arising from the A2 group.

The autoradiographic studies showed that the ventral medullary (A1) group projects to the locus coeruleus and to both major divisions of the dorsal vagal complex (Fig. 2A); subsequent double-labeling studies indicated that both of these pathways are primarily noradrenergic. The NST projects massively to the ventral medullary (A1) group (Fig. 2A), providing a possible route for visceral sensory information to reach the noradrenergic group projecting to vasopressinergic cells in the hypothalamus. Double-labeling experiments with True Blue injections centered in the A1 region and counterstaining with dopamine-β-hydroxylase confirmed that this pathway arises, in part at least, in the NST, but

that it is primarily non-noradrenergic, although some noradrenergic cells in the area postrema were doubly labeled (*14*).

These results indicate that a series of interrelated central noradrenergic pathways play an important role in the relay of visceral sensory information to the hypothalamus by way of the NST (Fig. 2A). The projection of the NST to parvicellular parts of the PVN is primarily noradrenergic, and non-noradrenergic cells in the NST project to another noradrenergic cell group (A1), which in turn innervates vasopressinergic parts of the PVN and SON. Hence, separate noradrenergic inputs may simultaneously influence neuroendocrine and autonomic modes of hypothalamic regulation (through the A1 group) or may influence the autonomic mode alone (through the A2 group). Since the projection from the locus coeruleus is confined to the periventricular part of the nucleus it may rather selectively modulate anterior pituitary function (*3*).

Because the NST receives visceral sensory information from cranial nerves IX and X, the circuitry outlined in Fig. 2 may be involved in a wide range of visceral responses. For example, considerable physiological evidence suggests that it plays an important role in the regulation of blood pressure and volume. Information from atrial stretch receptors, aortic baroreceptors, and carotid body chemoreceptors, which is relayed by these nerves, influences the secretion of vasopressin (*15*), as may inputs from osmoreceptors in the hepatic portal venous bed (*16*). Such information has been thought to affect vasopressin release through a direct projection from the NST or through a disynaptic route involving the parabrachial nucleus (*17*). The present results indicate, instead, that visceral information reaches vasopressinergic neurons in the hypothalamus by way of the A1 group (see Fig. 2A). Of course, it remains to be determined whether the dendrites of magnocellular neurons extend into parvicellular parts of the PVN and whether cells in the parvicellular division project to the magnocellular division.

Because overlapping inputs to specific parts of the parvicellular division of the PVN arise in the A1 and A2 groups, both regions may influence outputs from the PVN to spinal and medullary autonomic centers (Fig. 2B), pathways that act in concert with vasopressin release during homeostatic responses in the cardiovascular system. It has been shown (*6*) that increased blood pressure due to vasopressin release and tachycardia due to reciprocal changes in parasympathetic and sympathetic tone are elicited by electrical stimulation of the PVN, and that the PVN maintains a tonic inhibitory control over the heart rate component of the carotid sinus reflex. Central noradrenergic pathways may also be involved in several types of hypertension in animals, as well as in man (*18*), and the hypotensive actions of the α-noradrenergic agonist clonidine may be due in part to an effect on these pathways (*19*).

Our results are thus consistent with a substantial body of evidence linking the NST, the ventral medulla, and the PVN and SON to the regulation of peripheral cardiovascular homeostasis. Changes in peripheral blood pressure may also be accompanied by coordinated changes in the intracerebral microvasculature. The circuitry we have outlined here may be directly involved in such integration as well, since stimulation of the locus coeruleus, which receives a direct input from the A1 group, affects intracerebral blood flow and capillary permeability (*20*).

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10. In the cat the A1 cell group lies close to, but not within, the lateral reticular nucleus [W. W. Blessing, P. Frost, J. B. Furness, *Brain Res.* **192**, 69 (1980)]. We confirmed this observation in the rat by retrogradely labeling the lateral reticular nucleus with large injections of True Blue in the cerebellum and counterstaining the sections with antiserum to dopamine-β-hydroxylase.
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Ice-Rafting, An Indication of Glaciation?

In an otherwise excellent article, Herman and Hopkins (*1*) appear to believe in the old myth that ice-rafted material in deep-sea sediments indicates glaciation in the surrounding continents, and can be used to date the onset of such glaciations.

In fact, most ice-rafted material in marine sediments probably comes from coastal winter ice, where both the area and the possibilities for picking up material are far greater than in a glacier (*2*). Today there is a considerable amount of sediment ice-rafting around Denmark, without any glaciation (*3*). There are some exceptions from this rule: (i) During an Antarctic-type glaciation there will be too little ice-free coast for the formation of winter ice; (ii) at the very southern limit of ice-rafted material (*in*

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