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Glutamatergic transmission in the nucleus tractus solitarii: from server to peripherals in the cardiovascular information superhighway

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Abstract

Afferent nerves carrying signals from mechanoreceptors in the aortic arch and carotid sinus terminate predominantly in the nucleus tractus solitarii (NTS). Signal transduction and neurotransmission in the NTS are critical for central cardiovascular reflex control, but little was known about either until the late 1970's. None of the numerous neuroactive chemicals found in the NTS had met strict criteria as a neurotransmitter in the baroreflex arc until data suggested that the excitatory amino acid L-glutamate (GLU) might be released from baroreceptor afferent terminals in the NTS. In anesthetized animals microinjection into the NTS of GLU, which can be demonstrated in terminals in the NTS, produces cardiovascular responses like those seen with activation of the baroreceptor reflex. Similar responses occur in awake animals if the chemoreceptor reflex is eliminated; otherwise, in conscious animals responses mimic those of chemoreceptor reflex activation. GLU is released in the NTS upon selective activation of the baroreceptor, and possibly the chemoreceptor, reflex. Responses to selective agonists as well as baroreflex responses are eliminated by GLU antagonists microinjected into the NTS. Non-NMDA (*N*-methyl-D-aspartic acid) receptors seem to predominate at primary baroreceptor synapses in the NTS while NMDA receptors may be involved at later synapses. Although inhibition of soluble guanylate cyclase attenuates responses to ionotropic glutamate agonists in the NTS, nitric oxide does not seem to play a role in glutamate transmission in the NTS. GLU may also participate in transmission at cardiovascular neurons beyond the NTS. For example, a role has been suggested for GLU in the ventrolateral medulla and spinal cord. Work continues concerning GLU signal transduction and mechanisms that modulate that transduction both at the NTS and at other cardiovascular nuclei.

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Our understanding of central pathways in the baroreceptor reflex arc has increased remarkably over the past twenty-five years. From early observations that afferent nerve fibers of arterial baroreceptors terminated predominantly in the nucleus tractus solitarii (NTS) (1,2), it became apparent that the NTS plays a critical role in cardiovascular regulation. Destructive lesions (3) or chemical perturbations (4) of the nucleus led to interruption of the baroreceptor reflex and acute fulminating hypertension that was often fatal. However, experimental animals and humans that had sustained lesions of the NTS and survived were left with characteristically labile arterial blood pressures that were markedly responsive to environmental stimuli and naturally occurring behaviors (5-7). The acute hypertension attendant to NTS lesions was mediated in great measure by activation of the sympathetic nervous system and associated arterial vasoconstriction (3,8), but pathways by which the NTS connects to preganglionic sympathetic neurons in the intermediolateral column of the spinal cord remained to be determined.

Now it is well known that the NTS alters sympathetic function through its stimulatory influences on the caudal ventrolateral medulla (CVLM) which, in turn, projects to and inhibits cardiovascular neurons of the rostral ventrolateral medulla (RVLM) (9-11). The latter neurons of the RVLM provide critical excitatory influences upon the preganglionic sympathetic neurons (12-14).

Given that the NTS is the initial central site for processing incoming arterial baroreceptor signals, identification of a neurotransmitter released by baroreceptor afferent terminals in the NTS was of clear importance. Interestingly, an early experiment (4) designed to evaluate the effects of NTS dysfunction on regulation of arterial pressure led to the recognition that binding sites for excitatory amino acids may be present in the NTS and may contribute to central cardiovascular control. That experiment showed that bilateral injection into the NTS of low concentrations of the glutamate analog kainic acid led to initial depressor responses, like those seen with baroreflex activation, but then led to extreme fulminant hypertension, pulmonary edema and death.

In testing the hypothesis that an excitatory amino acid may be a transmitter of baroreceptor afferents, it was found that unilateral microinjection of glutamate itself into the NTS of anesthetized animals elicited depressor and bradycardic responses that were qualitatively like those observed with activation of baroreceptor afferent nerves (15). At the time of that initial report there was much skepticism about a transmitter role for glutamate because the compound uniformly activated central neurons. However, credence was given to the hypothesis because high affinity uptake of glutamate into synaptosomal fractions from the NTS was reduced in animals that had undergone unilateral removal of the nodose ganglion, the site of neurons of origin of baroreceptor afferents (16). While the physiologic observations were reported by investigators in many laboratories around the world, several carefully controlled studies (17,18) showed that the high affinity uptake for glutamate was not affected by nodose ganglionectomy. Rigorous studies were begun to seek to determine if glutamate satisfied accepted criteria for neurotransmitters in specific neuronal pathways (Table 1) (19).

Early in the course of these studies there were few selective and specific glutamate receptor antagonists available but experiments with one antagonist, glutamate diethylester, showed that the compound, when injected into the NTS, blocked responses to subsequent injection of glutamate and blocked baroreceptor reflexes as well (20,21). Studies that dealt more selectively with receptor interactions were needed because of the growing recognition that there were numerous glutamate receptor subtypes. Among these, the ones that have been best charac-

terized include the ionotropic *N*-methyl-D-aspartic acid (NMDA), kainic acid (KA), and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors and the metabotropic *trans*-1-amino-1,3-cyclopentane dicarboxylic acid (ACPD) receptors (22,23).

Evolving studies have suggested a role for each receptor type in baroreflex signal transduction in the NTS. Like glutamate itself, agonists for each of the receptor subtypes were found to elicit baroreflex-like responses when microinjected unilaterally into the NTS (24-26). Thus, the identity of action criterion seemed satisfied, but experiments in conscious freely moving animals caused some uncertainty (27). In the awake animal injections of glutamate into the NTS elicited pressor responses and bradycardia, not depressor responses, as in the anesthetized model. However, a recent study (27) suggests that the pressor response elicited in conscious animals may depend upon activation of neurons in chemoreflex pathways and resulting pressor actions take precedence over depressor responses to activation of baroreflex neurons.

In general, then, studies showed that administration of exogenous glutamate and glutamate receptor agonists into the NTS elicits responses that mimic baroreflex activation but it was important to demonstrate that endogenous stores of glutamate are present in the NTS. Indeed, several studies have shown not only that glutamate is present in the NTS but also that the concentrations of glutamate exceed those of some other amino acids and are comparable to concentrations found in brain regions where glutamate is acknowledged to be a transmitter (16,28). More recent studies have employed immunohistochemical techniques and confirmed that glutamate-containing nerve terminals are present in the NTS (29); and some others, using retrograde labeling with [^{3}H]-D-aspartate have found that afferent projections from the nodose ganglion into the NTS are glutamatergic (30). Thus, glutamate satisfies the criterion that a transmitter of specific nerve terminals must be demonstrated at those terminals. Nonetheless, further studies were needed to determine if the putative transmitter was released from those terminals.

Table 1 - Glutamate in the NTS and criteria* for a neurotransmitter.

*Criteria modified from Orrego (19).

Content	Present (suggested local synthesis)
Release	*In vivo* with baroreflex and *in vitro* with K^+
Receptors	Multiple subtypes in NTS
Identity of action	Responses like baroreflex
Means of inactivation	High affinity uptake
Antagonists and transmission	Selective antagonists block baroreflex
Identity of blockade	Antagonists block reflex but not glutamate

Very early studies *in vivo* showed that glutamate was released into the NTS upon stimulation of vagus nerve afferents (31,32) and one study suggested that the amino acid that was released was synthesized locally (33). Subsequent studies *in vitro* suggested that glutamate, but not aspartate, was released from neurotransmitter pools in the NTS in that release was stimulated by potassium and was dependent on extracellular calcium (28). Although these studies supported release from terminals in the NTS, none of them directly addressed the question of whether glutamate that was released might derive from vagus (or glossopharyngeal) nerve terminals in general or specifically from baroreceptor afferent terminals. One laboratory did not detect release of glutamate with baroreceptor reflex stimulation (34). However, two laboratories have now found that selective stimulation of arterial baroreceptors does cause release of glutamate into the medial region of the intermediate (or cardiovascular) NTS (35,36).

Thus, the amino acid is not only present at the terminals but also is apparently released from those terminals when the baroreceptor reflex is activated. Upon release of a transmitter, actions of that transmitter must

be limited in some way. Inactivation occurs by spontaneous or enzymatic breakdown with some interneuronal messengers and by high affinity uptake for others such as glutamate. Although different investigators have drawn conflicting conclusions about the relationship between high affinity uptake and vagus nerve terminals, there is no dissent that a high affinity uptake mechanism that would inactivate glutamate upon its release is present in the NTS (16-18).

There is now also ample evidence that receptors at which the glutamate could act are found in the NTS (37-39). With denervation of the nucleus by removal of the nodose ganglion, there is upregulation of those receptors (40). Deafferentation also leads to development of augmented physiologic responses to microinjection of exogenous glutamate into the NTS (41). Both phenomena are consistent with denervation supersensitivity that would be observed when an endogenous transmitter is no longer released upon target postsynaptic membranes and their receptors.

The sum total of the autonomic responses to glutamate activation of the NTS are the changes in arterial pressure and heart rate that were described previously but recent work has shown that complex hemodynamic effects accompany these changes (42). In the renal and mesenteric vascular beds, arterial vasoconstriction predominates while prominent arterial vasodilatation occurs in hindquarter arteries. Alpha receptor antagonists block the vasoconstriction, but with the addition of inhibitors of nitric oxide synthase, the vasodilatation is blocked as well (43). Thus, glutamate acting at receptors in the NTS not only elicits changes in blood pressure, heart rate and sympathetically mediated vasoconstriction, but may also lead to release of nitric oxide or nitrosyl factors that contribute to hindlimb vasodilatation.

Considerable effort has gone into defining what glutamate receptor subtypes in the NTS might mediate these responses. When kynurenic acid, which is a selective antagonist for glutamate receptors, was bilaterally injected into the NTS it blocked the baroreflex (25,26). However, while the antagonist was found to have blocked responses to NMDA, KA, and AMPA it did not block those to QUIS (quisqualate) or glutamate itself (25,26). These observations not only suggest the possibility that an endogenous agonist other than glutamate might act through excitatory amino acid receptors in the NTS, but they also suggest that both ionotropic and metabotropic glutamate receptors may participate in actions of glutamate and in transmission of baroreflex signals in the NTS. Electrophysiological studies strongly supported a role for non-NMDA receptors, but not NMDA receptors, at the first synapse of baroreflex afferents in the NTS (44). Now considerable evidence has supported a role, possibly at presynaptic membranes, for metabotropic glutamate receptors as well (45,46). Although there was doubt at one time that NMDA receptors were directly involved in central baroreflex transmission in the NTS, recent evidence indicates that they, as well as non-NMDA receptors, are integral to the reflex arc (47). Specifically, the gain of the baroreflex is reduced after bilateral injection into the NTS of either the NMDA antagonist MK-801 or the non-NMDA antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX). Reduction of the gain of the reflex is additive when both antagonists are combined. It is quite probable that the two receptor subtypes are concentrated on neurons at different positions in the central pathway. Non-NMDA receptors likely predominate at the primary synapse while NMDA receptors are more likely responsible for transmission at subsequent interneuronal synapses in the NTS (48).

Baroreflex signal transduction beyond the glutamate receptor has not been extensively studied but recent studies suggest that activation of ionotropic glutamate receptors leads to activation of soluble guanylate cyclase

and production of cyclic GMP (49). This finding suggests that actions of glutamate in the NTS are related to release of nitric oxide (50,51), but microinjection of nitric oxide itself into the NTS does not elicit cardiovascular responses and those nitric oxide donors that do produce cardiovascular responses do so independent of their release of nitric oxide (52).

After processing the transmitter signals in the NTS, neuronal impulses related to baroreceptor activity pass from the NTS to the CVLM where glutamate transmission is effected through NMDA and non-NMDA receptors (53,54). The CVLM activation leads in turn to GABA-mediated inhibition of the tonic vasomotor influences of the RVLM, but even RVLM may be influenced by descending hypothalamic glutamatergic pathways that can be blocked by kynurenic acid (55).

Glutamate even seems to be involved in the final central synapse in the sympathetic limb of the baroreflex. Considerable evidence points to glutamate as the active agent released from fibers of the RVLM as they terminate on preganglionic neurons in the spinal cord (56,57), and others have shown that effects are mediated through actions at both NMDA and non-NMDA receptors (58-60).

In summary, the accumulated data of twenty-five years of study suggest that L-glutamate may act at multiple synapses in central pathways of the arterial baroreflex. At some synapses, an endogenous ligand other than glutamate may be the transmitter responsible for the physiologic responses to naturally occurring stimulation of the baroreflex, but that transmitter, whether glutamate or one of its analogs, acts at excitatory amino acid receptors in transducing the reflex signals. The potential pathologic implications of disturbances in glutamate transmission have not been fully appreciated, but clear alterations in glutamate transmission do seem to occur at multiple synapses in the baroreflex arc in some models of spontaneous hypertension (61-66).

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