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Autonomic processing of the cardiovascular reflexes in the nucleus tractus solitarii

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Abstract

The nucleus tractus solitarii (NTS) receives afferent projections from the arterial baroreceptors, carotid chemoreceptors and cardiopulmonary receptors and as a function of this information produces autonomic adjustments in order to maintain arterial blood pressure within a narrow range of variation. The activation of each of these cardiovascular afferents produces a specific autonomic response by the excitation of neuronal projections from the NTS to the ventrolateral areas of the medulla (nucleus ambiguus, caudal and rostral ventrolateral medulla). The neurotransmitters at the NTS level as well as the excitatory amino acid (EAA) receptors involved in the processing of the autonomic responses in the NTS, although extensively studied, remain to be completely elucidated. In the present review we discuss the role of the EAA L-glutamate and its different receptor subtypes in the processing of the cardiovascular reflexes in the NTS. The data presented in this review related to the neurotransmission in the NTS are based on experimental evidence obtained in our laboratory in unanesthetized rats. The two major conclusions of the present review are that a) the excitation of the cardiovagal component by cardiovascular reflex activation (chemo- and Bezold-Jarisch reflexes) or by L-glutamate microinjection into the NTS is mediated by N-methyl-D-aspartate (NMDA) receptors, and b) the sympatho-excitatory component of the chemoreflex and the pressor response to L-glutamate microinjected into the NTS are not affected by an NMDA receptor antagonist, suggesting that the sympatho-excitatory component of these responses is mediated by non-NMDA receptors.

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- AP-5
- Kynureic acid

Introduction

The nucleus tractus solitarii (NTS) is the first synaptic station of the cardiovascular afferents in the central nervous system (CNS) and plays a key role in the modulation of the autonomic efferent activity to the cardiovascular system. Among the major cardiovascular afferent systems involved in the autonomic regulation of arterial pressure, the afferents of the carotid and aortic baroreceptors (baroreflex), the carotid chemoreceptors (chemoreflex) and the cardiopulmonary afferent C-fibers (Bezold-Jarisch reflex) all have their first synapse in the NTS. The different information from the periphery is processed in the NTS in order to produce the proper autonomic response, in accordance with the adjustments required to normalize arterial blood pressure. Activation of the arterial baroreflex or Bezold-Jarisch reflex increases the parasympathetic activity to the heart and reduces the sympathetic drive to the heart and vessels in order to bring arterial blood pressure back to the normal level. On the other hand, the activation of the chemoreflex, in addition to the ventilatory adjustments, produces cardiovascular changes characterized by an increase in the sympathetic and parasympathetic activity, with a consequent increase in arterial pressure and an intense bradycardic response (1,2).

The activation of these cardiovascular afferents probably releases excitatory amino acids (EAA) at the level of the NTS neurotransmitter(s), which produce excitation of different postsynaptic neurons projecting from the NTS to other areas of the brain stem involved in the generation and control of the autonomic activity. The projections from the NTS to the nucleus ambiguus, when activated, produce the excitation of parasympathetic preganglionic neurons located in this area with a consequent increase in the vagal drive to the heart. The projection related to the parasympathetic pathways seems to be involved in the baro-, chemo- and Bezold-Jarisch reflexes, since the activation of these afferents produces bradycardic responses similar to that observed in response to chemical or electrical stimulation of the nucleus ambiguus (2-5).

The sympatho-inhibitory pathways of the baro- and Bezold-Jarisch reflexes involve an excitatory projection from the NTS to the caudal ventrolateral medulla (CVLM) and an inhibitory projection from the CVLM to the rostral ventrolateral medulla (RVLM), which is the site of neurons that generate the sympathetic vasomotor tone (6). The activation of this neuronal pathway by baro- or Bezold-Jarisch reflex afferents results in sympatho-inhibition and a consequent fall in arterial pressure (7-9). On the other hand, the activation of the peripheral chemoreceptors produces sympatho-excitation probably by the activation of a direct and/or indirect projection from the NTS to the RVLM, resulting in an increase in arterial pressure. Despite the lack of anatomical evidence in favor of these direct projections from the NTS to the RVLM, functional and anatomical studies have indicated the existence of direct projections from the NTS to RVLM (10,11).

Several experimental lines of evidence concerning neurotransmission of the afferent information of the cardiovascular reflexes in the NTS support the hypothesis that L-glutamate, an EAA, is the neurotransmitter released by the afferents of baro-, chemo, and Bezold-Jarisch reflexes in the NTS and, despite some controversy (12-14), this amino acid remains the strongest candidate for the role of neurotransmitter of the baroreflex (15,16), chemoreflex (8,17) and Bezold-Jarisch reflex (5,18). Assuming that L-glutamate is in fact the neurotransmitter in the NTS, the question that naturally arises is: how can the same EAA generate opposite autonomic responses such as sympatho-inhibition during baroreflex activation or sympatho-excitation during chemoreflex activation (8,17) at the NTS level? To address this question it is essential to consider not

only L-glutamate itself but also the different subtypes of ionotropic receptors (N-methyl-D-aspartate (NMDA), kainate, AMPA/quisqualate), which may be located on different postsynaptic neurons associated with different pathways from the NTS to other areas in the brain stem involved in the excitation or inhibition of sympathetic activity in the RVLM.

Before discussing the different subtypes of EAA receptors involved in the autonomic responses to the activation of the chemo- and the Bezold-Jarisch reflex, the effect of L-glutamate microinjection into the NTS of conscious freely moving rats in comparison with the effect of the same microinjection into the NTS of anesthetized rats should be emphasized. This aspect became relevant in the evaluation of the role of L-glutamate in neurotransmission in the NTS because microinjection of L-glutamate into the NTS of unanesthetized rats produced an increase in arterial pressure (19) instead of the expected depressor response, as previously demonstrated in anesthetized rats (12,13,15). The qualitative difference between the cardiovascular responses to L-glutamate microinjection into the NTS of conscious *vs* anesthetized rats is important, since most of the support for the concept that L-glutamate may be the neurotransmitter of the baroreflex at the NTS level originated from studies performed under anesthesia.

The following aspects related to glutamatergic neurotransmission in the NTS will be discussed in the present review: a) characterization of the cardiovascular response to L-glutamate microinjected into the NTS of conscious rats as well as the subtypes of EAA receptors involved in these responses; b) effects of previous local microinjection of glycine, an inhibitory amino acid, on the cardiovascular responses to L-glutamate microinjected into the NTS; c) the subtypes of EAA receptors involved in the cardiovascular responses to chemoreflex activation with potassium cyanide (KCN); d) subregions of the commissural NTS involved in the processing of the baro- and chemoreflex afferents, and e) the subtypes of EAA receptors involved in the cardiovascular responses to Bezold-Jarisch reflex activation with serotonin (5-HT).

Characterization of the cardiovascular response to L-glutamate microinjected into the NTS of conscious rats and the subtypes of EAA receptors involved in these responses

The NTS has been used as a model system for examining mechanisms of cardiovascular afferent processing within the CNS since the study by Miura and Reis (20) demonstrating that electrolytic lesion of this area produced fulminating hypertension. With respect to the neurotransmission of the baroreceptor afferents in the NTS and especially the role of L-glutamate in this neurotransmission, the first evidence that the microinjection of this EAA into the NTS produces responses similar to those obtained by baroreceptor activation was reported by Talman et al. (15). Since this study, considerable pharmacological, physiological and neurochemical evidence has supported the hypothesis that the excitatory amino acid L-glutamate is a neurotransmitter released by baroreceptor afferent nerve terminals in the NTS (14). Pharmacological studies have demonstrated that administration of L-glutamate into the NTS of anesthetized animals produces depressor and bradycardic responses similar to those obtained by activation of arterial baroreceptor afferents (12,13,15,21, 22). Neurochemical studies have demonstrated high-affinity uptake of glutamate, indicating the existence of glutamatergic nerve terminals and a mechanism for inactivation of endogenously released glutamate in the NTS (23,24). Other studies have also shown that glutamate is released in the NTS during stimulation with high potassium levels *in vitro* and *in vivo* as well as during electrical

stimulation of the vagus afferent *in vivo* (25-28). More recently, studies by Ohta et al. (29) have shown that activation of the baroreflex releases L-glutamate in the NTS.

Removal of the nodose ganglion, the site of origin of vagal visceral afferents to the NTS (30), has been shown to lead to central degeneration of these afferents (23). In addition, other studies have shown an immediate reduction in the release of endogenous glutamate into the NTS by removal of the nodose ganglion (31) and increased binding affinity to glutamate receptors in the NTS approximately two weeks after unilateral removal of the nodose ganglion (32). In anesthetized rats, the hypotensive response to microinjection of L-glutamate into the NTS was significantly augmented 10 days after removal of the nodose ganglion (22), supporting the concept that L-glutamate and its receptors are involved in this neurotransmission. Taken together, these data are consistent with the hypothesis that glutamate is an integral transmitter of vagal baroreceptor afferents terminating in the NTS.

EAA play an important role in the transmission of baroreceptor reflex and arterial chemoreceptor reflex as well as in the Bezold-Jarisch reflex pathways in the NTS (5,8,18, 33). However, the subtypes of receptors involved in these reflexes and whether L-glutamate is the neurotransmitter of the cardiovascular afferents in the NTS remain controversial. Studies by Leone and Gordon (12) and Talman (13) have shown that kynurenic acid microinjected into the NTS blocked the response to NMDA, kainic acid and AMPA as well as the baroreflex and the responses elicited by electrical stimulation of the aortic depressor nerve. However, the authors showed that microinjection of kynurenic acid into the NTS prior to L-glutamate produced no blockade of the cardiovascular responses to the microinjection of L-glutamate into the NTS and suggested that the neurotransmitter of the baroreceptor afferents in the NTS could be an EAA or EAA analog other than L-glutamate. On the other hand, studies by Le Galloudec et al. (34), also performed on anesthetized rats, demonstrated that kynurenic acid was effective in blocking the cardiovascular responses to L-glutamate microinjected into the NTS. These differences may be related to the fact that those experiments were performed under different anesthetic conditions, which may have altered the effect of both agonists and antagonists of EAA receptors in the NTS.

Since anesthesia may affect neurotransmission at the NTS level by an unknown mechanism, we decided to use in our experiments the unanesthetized model developed and standardized by Michelini and Bonagamba (35). Using this method, we demonstrated (19) that microinjection of L-glutamate into the NTS produced a dose-dependent pressor response in contrast to the dose-dependent depressor response observed in the same animals under chloralose or urethane anesthesia, indicating the strong influence of anesthesia on the pathways activated by L-glutamate within the NTS. The different cardiovascular responses to the microinjection of L-glutamate into the NTS of conscious and anesthetized animals may be associated with the effect of the anesthetics on the chemoreflex pathway originating in the NTS. Under anesthesia the chemoreflex pathway seems to be deeply affected and the pressor response is blocked. Therefore, we suggested that under anesthetized conditions the effect of L-glutamate may be linked more to the activation of the baroreflex pathways (a fall in pressure), while under unanesthetized conditions the activation of the chemoreflex pathways predominates (pressor response).

In another study (16), we performed microinjection of increasing doses of L-glutamate into the NTS of conscious rats and observed a dose-dependent pressor and bradycardic response. In order to study the mechanisms involved in the responses to L-glutamate microinjection into the NTS, se-

lective autonomic blockade was also performed. Intravenous treatment with methylatropine blocked the bradycardic response to L-glutamate microinjected into the NTS and the pressor response observed was significantly enhanced (16). In contrast, the α_1-adrenergic blockade with prazosin virtually abolished the pressor response to L-glutamate, but produced no changes in the bradycardic response, demonstrating that bradycardia was not secondary to the activation of the baroreflex. These findings indicate that microinjection of L-glutamate into the NTS of unanesthetized rats activates parasympathetic (bradycardia) and sympathetic (pressor responses) pathways in an independent manner, showing a dissociation between these two autonomic projections from the NTS.

In the study by Colombari et al. (16) we blocked in a dose-dependent manner both pressor and bradycardic responses to L-glutamate microinjection into the NTS by previous local administration of increasing doses of kynurenic acid, a non-selective antagonist of EAA receptors. The data indicated that both pressor and bradycardic responses to microinjection of exogenous L-glutamate into the NTS of unanesthetized rats were effectively mediated by EAA receptors in the NTS. In addition, we were also able to block the reflex bradycardia induced by pressor doses of phenylephrine (*iv*), indicating that at least the parasympathetic component of the arterial baroreflex is mediated by EAA receptors at the NTS level.

In order to evaluate the role of the different subtypes of ionotropic receptors in the cardiovascular responses produced by microinjection of L-glutamate into the NTS, we demonstrated (36) that previous microinjection of AP-5, a selective NMDA receptor antagonist, into the NTS of unanesthetized rats produced a dose-dependent blockade of the bradycardic response and no effect on the pressor response. These data indicate that the activation of the cardiac parasympathetic drive to the heart (bradycardia) by L-glutamate involves the activation of NMDA receptors and suggest that the activation of the sympatho-excitatory component (pressor response) by L-glutamate in the NTS is mediated by non-NMDA receptors.

Effects of previous local microinjection of glycine, an inhibitory amino acid, on the cardiovascular responses to L-glutamate microinjected into the NTS

Talman and Robertson (37) have shown that the cardiovascular responses produced by microinjection of L-glutamate into the NTS of anesthetized rats were significantly reduced by previous local microinjection of the inhibitory amino acid glycine, which is the major inhibitory amino acid in the CNS. Pharmacological studies have shown that glycine may act on NMDA receptors as a co-agonist of this receptor subtype (38). Since glycine affected the cardiovascular response to L-glutamate microinjected into the NTS of anesthetized rats (37) and NMDA is involved in the bradycardic response to L-glutamate microinjected into the NTS of unanesthetized rats (36), we recently performed studies in order to determine the possible changes in the pressor and bradycardic responses to L-glutamate microinjected into the NTS produced by previous local microinjection of increasing doses of glycine (39). Surprisingly, the data showed that glycine mainly produced a dose-dependent blockade of the pressor response to L-glutamate while the bradycardic response was only partially reduced, but not in a dose-dependent manner.

In contrast to the studies by Talman and Robertson (37) performed on anesthetized rats in which both depressor and bradycardic responses to L-glutamate after glycine were affected, in our study the effect of glycine was not evident on the bradycardic component of the responses but the pressor compo-

nent was abolished. Our data suggest that glycine has a greater neuromodulatory effect on the EAA receptors related to the sympathoexcitatory component (pressor response) than on the parasympathetic component (bradycardia) activated by L-glutamate microinjection into the NTS. The differences between our data and the findings by Talman and Robertson (37) are again probably related to the anesthetized *vs* unanesthetized conditions of the rats. Studies on unanesthetized rats to determine the role of glycine in the neurotransmission/neuromodulation of the baro- and chemoreflexes are required to improve our understanding of the effective role of this inhibitory amino acid in the NTS.

Subtypes of EAA receptors involved in the cardiovascular responses to chemoreflex activation with potassium cyanide

The activation of the arterial chemoreflex produces respiratory as well as cardiovascular adjustments (1,40). The activation of the chemoreflex by intravenous injection of KCN into unanesthetized animals produced an increase in arterial pressure, bradycardia and tachypnea in a dose-dependent manner. These responses to KCN are essentially dependent on the stimulation of carotid chemoreceptors because bilateral ligature of the carotid body artery abolished both the cardiovascular and respiratory responses to KCN injection (2,41,42). The cardiovascular responses induced by KCN result from the activation of two independent autonomic mechanisms: 1) a sympathetic pathway related to the pressor response which was blocked by intravenous injection of prazosin, an α_1-adrenoceptor antagonist, and 2) a parasympathetic pathway related to the bradycardic response which was abolished only after intravenous injection of methyl-atropine, a cholinergic receptor antagonist (2,41,42). Therefore, the pattern of the cardiovascular responses to chemoreflex activation resembles the cardiovascular responses obtained after microinjection of L-glutamate into the NTS of conscious freely moving rats.

The cardiovascular responses to chemoreflex activation with KCN may vary with the type of anesthetic used as well as with the level of anesthesia. Studies by Franchini and Krieger (42) have shown that the pressor response produced by KCN in unanesthetized rats was abolished under urethane or pentobarbital anesthesia, and in the case of chloralose anesthesia the pressor response was converted to a depressor response (unpublished data from our laboratory). This is an important aspect to be considered in studies on the neurotransmission of the chemoreflex because most of such studies on the NTS of rats were performed under anesthesia (8,17). Also, these studies did not consider the changes in heart rate in response to chemoreflex activation because under anesthesia these changes are negligible, while in unanesthetized rats chemoreflex activation produces an intense bradycardic response (2,41,42).

Studies performed by Vardhan et al. (8) in anesthetized rats demonstrated that selective blockade of NMDA receptors in the NTS produced no blockade of the pressor response induced by the chemoreflex. However, the changes in heart rate were not evaluated, probably because the variations of this parameter were blunted by the effect of anesthesia. In order to determine the role of NMDA receptors in the neurotransmission of the chemoreflex in the NTS, especially in the cardiac parasympathetic component of this reflex, we performed bilateral microinjection of increasing doses of AP-5, a selective NMDA receptor antagonist, into the NTS of unanesthetized rats (2). The data showed that bilateral microinjection of AP-5 into the NTS produced a dose-dependent reduction in the bradycardic response of the chemoreflex, whereas the pressor and tachypneic responses induced by intravenous

KCN injection were not affected. These data indicate that the cardiac parasympathetic component of the chemoreflex in the NTS is mediated by NMDA receptors and suggest that the sympatho-excitatory and ventilatory components of this reflex are mediated by non-NMDA receptors.

These chemoreflex data indicating that the cardiac parasympathetic component of the chemoreflex is mediated by NMDA receptors at the NTS level are similar to those reported previously in relation to the microinjection of L-glutamate into the NTS (36), which showed that the bradycardic response was also blocked in a dose-dependent manner by AP-5. The dissociation between the processing of the different autonomic components at the NTS level observed in our studies agrees with the data of Mifflin (43) who demonstrated that the neurons in the NTS do not integrate the chemoreceptor afferent inputs in a homogeneous manner, suggesting that the different components of this reflex (i.e., pressor response, bradycardia and tachypnea) might be mediated by different neurons, and also by different subtypes of excitatory amino acid receptors. Another important aspect related to the cardiovascular responses to microinjection of L-glutamate into the NTS or to the activation of the chemoreflex in unanesthetized rats is the similarity of the pressor and bradycardic responses obtained in both experimental conditions. This similarity supports the hypothesis that the pressor response to L-glutamate microinjection into the NTS of unanesthetized rats is related to the activation of the chemoreflex pathways at the NTS level.

A study by Mizusawa et al. (44) has shown that L-glutamate is released in the NTS during the stimulation of the carotid chemoreceptors and several other studies have also shown that the pressor response to chemoreflex activation was blocked by EAA receptor antagonists microinjected into the NTS (8,17), indicating that EAA receptors are directly involved in the sympatho-excitatory component of this reflex in the NTS. Therefore, it is possible that microinjection of L-glutamate into the NTS of unanesthetized rats produces cardiovascular responses by the activation of the same pool of EAA receptors located in post-synaptic neurons of the chemoreflex pathways.

Subregions of the commissural NTS involved in the processing of the baro- and chemoreflex afferents

Anatomical studies (45-47) have shown that the carotid chemoreceptor afferents terminate in the NTS and a physiological study (8) has indicated that this termination occurs in the midline portion of the commissural NTS, an area close to the lateral commissural NTS in which most of our sites of microinjection of L-glutamate or its different antagonists were located. The microinjection of L-glutamate into the lateral commissural NTS (16,19) as well as into the intermediate NTS (48) produces pressor and bradycardic responses. Electrolytic lesion of the medial commissural NTS abolished the cardiovascular responses to chemoreflex activation with KCN and the pressor response to L-glutamate microinjection into the intermediate NTS, which was converted to a depressor response (48). In addition, this study by Colombari et al. (48) demonstrated that lesion of the midline portion of the commissural NTS abolished the chemoreflex while preserving the baroreflex, indicating that at the level of the medial commissural and intermediate NTS, there is a complex interaction of the afferents of baro- and chemoreflexes. This interaction became demonstrable after lesion of the medial commissural NTS when the microinjection of L-glutamate into the intermediate NTS produced a fall in pressure instead of the increase in pressure observed in intact animals. These data are in accordance with other studies and support the hypothesis that the processing of the chemoreflex afferents

in the NTS occurs mainly in the medial commissural NTS. However, further investigations are required to identify the mechanisms involved in the processing of the sympatho-excitatory component (pressor response) of the chemoreflex, especially in unanesthetized rats.

Subtypes of EAA receptors involved in the cardiovascular responses to Bezold-Jarisch reflex activation with serotonin

The activation of the cardiopulmonary afferent C-fibers by chemical substances such as serotonin or phenylbiguanide produces hypotension, bradycardia and apnea, a pattern of responses characterized as the Bezold-Jarisch reflex (49-51). In anesthetized rats, the activation of the Bezold-Jarisch reflex produces intense bradycardia and a fall in pressure which is associated with a sharp reduction in sympathetic activity (18,52). In order to determine the role of NMDA receptors in the neurotransmission of the Bezold-Jarisch reflex in the NTS, we activated this reflex before and after bilateral microinjection of increasing doses of AP-5 into the NTS (5). AP-5 produced a dose-dependent blockade of both bradycardia and depressor responses in unanesthetized rats, suggesting that both autonomic components of the responses, i.e., sympatho-inhibition and cardiac parasympathetic excitation, were mediated by NMDA receptors. Since the fall in pressure in response to Bezold-Jarisch reflex activation could be driven by the intense bradycardic response, we blocked the cholinergic receptors with methyl-atropine, and under these experimental conditions the activation of the reflex produced no bradycardic response or fall in pressure. These data clearly indicate that the fall in pressure in response to Bezold-Jarisch reflex activation is driven by the bradycardic response, at least in conscious freely moving rats.

Therefore, the data obtained for unanesthetized rats indicate that the cardiac parasympathetic component of the Bezold-Jarisch reflex is also mediated by NMDA receptors at the NTS level. These data, taken together with those obtained with the microinjection of L-glutamate into the NTS and with those obtained by chemoreflex activation, indicate that the cardiac parasympathetic component originating at the NTS level is mediated by NMDA receptors.

Summary and perspectives

The data related to glutamatergic neurotransmission in the NTS of conscious freely moving rats presented in this review indicate that the microinjection of L-glutamate into the NTS of unanesthetized rats increases both pressure and bradycardic responses. In this case, both responses were blocked in a dose-dependent manner by kynurenic acid, a non-selective ionotropic receptor antagonist, indicating that the effects of L-glutamate in the NTS are effectively mediated by EAA receptors. The data also showed that the reflex bradycardic response to an increase in pressure induced by phenylephrine was also blocked by kynurenic acid. In another series of experiments, we demonstrated that the bradycardic response to L-glutamate microinjection into the NTS was mediated by NMDA receptors, considering that the bradycardic but not the pressor response was blocked in a dose-dependent manner by AP-5.

We also documented that local microinjection of glycine, an inhibitory amino acid, prior to L-glutamate into the NTS produced a dose-dependent blockade of the pressor response but not a dose-dependent blockade of the bradycardic response, indicating that this amino acid may play a major role in the neuromodulation of the sympatho-excitatory component of the response to L-glutamate.

The data also showed that the cardiac parasympathetic component (bradycardia) of the chemoreflex as well as of the Bezold-Jarisch reflex was blocked in a dose-depend-

ent manner by the NMDA receptor antagonist AP-5. The pressor component of the response to chemoreflex activation was not affected by an NMDA receptor antagonist, suggesting that this component may be mediated by non-NMDA receptors. Electrolytic lesion of the medial commissural NTS abolished the pressor response to chemoreflex activation and to the microinjection of L-glutamate into the NTS, indicating that this subregion of the NTS plays a critical role in the processing of the chemoreflex pathways in the NTS.

Taken together, these data indicate that the cardiovagal components of the chemo- and Bezold-Jarisch reflexes and the bradycardic response to L-glutamate microinjected into the NTS were mediated by NMDA receptors. Additional experiments are required in order to demonstrate whether the reflex bradycardic response to baroreceptor activation is also mediated by NMDA receptors. Since the reflex bradycardia to baroreceptor activation was blocked by kynurenic acid (16), we suggest that NMDA receptor antagonists will also block the reflex bradycadia to baroreceptor activation.

The NMDA receptor antagonist produced no change in the pressor component of the chemoreflex response, suggesting that this component of the chemoreflex may be mediated by non-NMDA receptors. To answer this question, it will be critical to perform experiments using selective (DNQx or CNQx) or non-selective (kynurenic acid) non-NMDA receptor antagonists to determine whether this pressor response associated with sympatho-excitation is mediated by non-NMDA receptors.

The present evidence in favor of the involvement of NMDA receptors in the processing of the parasympathetic component of the reflexes and the possibility that sympatho-excitatory and sympatho-inhibitory components of the different reflexes are mediated by different EAA receptor subtypes open new and interesting perspectives for the understanding of the autonomic processing of the cardiovascular afferents in the NTS.

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