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Neuronal Responses to Systemic Nicotine in the Solitary Tract Nucleus: Origin and Possible Relation with Nutritional Effects of Nicotine

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YETTEFTI, K., J. C. ORSINI AND J. PERRIN. *Neuronal responses to systemic nicotine in the solitary tract nucleus: Origin and possible relation with nutritional effects of nicotine.* PHARMACOL BIOCHEM BEHAV **58**(2) 529–535, 1997.—Single-unit activity was recorded extracellularly in the caudal part of the solitary tract nucleus of anesthetized rats. Of 60 recorded neurons, 44 (73.3%) responded to intravenous (IV) nicotine. The incidence of response was significantly greater in the cells sensitive to moderate changes in blood glucose level, suggesting that the effects of nicotine on food intake and body weight are partly mediated by the glycemia-sensitive neurons in the caudal nucleus tractus solitarius. Only one-fourth of the neurons affected by IV nicotine responded in the same direction to iontophoretic nicotine application, suggesting that sensitivity to systemic nicotine results mainly from an indirect mechanism. Based on the observed effects of nicotinic agonists and antagonists unable to cross the blood–brain barrier, a majority of indirect unit responses to IV nicotine might be mediated by peripheral receptors, while the remaining ones might involve central or both central and peripheral receptors.
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Nucleus tractus solitarius   Unit activity   Microiontophoresis   Nicotine   Glucose   Clonidine
Energy balance   Body weight   Feeding

CIGARETTE smokers weigh less than nonsmokers and, in general, weight gain occurs after smoking cessation (40). Inverse correlation has been found between administered nicotine doses and weight gain in the rat (33).

It has been reported that decrease in body weight gain accompanying nicotine administration does not result from a decrease in food intake in the rat (45) and that nicotine exposure via smoking in humans does not affect hunger, total caloric intake, or macronutrient or taste selection (41). Accordingly, the effect of nicotine on weight gain has been attributed to an increase in energy use (25), probably mediated by a decline in plasma insulin level (14,44). These observations conflict with other results suggesting that the weight lessening effect of nicotine is a result of either general anorectic effects (22,37,51,52) or a more specific decrease in the consumption of sweet-tasting foods (12,13). Probably either metabolic or behavioral factors, or both, are responsible for the nutritional action of the drug.

Consequently, the disturbance in body weight control induced by nicotine may be mediated by brain structures that control metabolic and/or behavioral regulation of the body's energy balance. Essential for this control are hypothalamic nuclei such as the lateral hypothalamic area (4) or the paraventricular nucleus (19), and the hindbrain areas (11). In the hindbrain, the caudal part of the nucleus tractus solitarius (NTS) receives nutrition-related signals from digestive interoceptors (1,2), and its adrenergic and noradrenergic ascending connections with the lateral hypothalamic area (42) and the paraventricular nucleus (8,9) probably contribute to the catecholaminergic modulation exerted on food intake through these nuclei (20,21). Both the caudal NTS and the lateral hypothalamic area are involved in glucoprivic eating (5,53). The

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neuronal sensitivity of these regions to glycemic fluctuations within the physiological range has been considered compatible with their involvement in nutritional adjustments (17,38, 57). Almost 50% of the glycemia-sensitive neurons in the lateral hypothalamic area have been found to respond to intravenous (IV) nicotine (18) and might mediate its nutrition-disturbing effects. However, the possible response to nicotine of the glycemia-sensitive neurons in the caudal NTS has not been investigated as yet. The NTS is sensitive to nicotine: systemic administration of the molecule has been found to induce c-fos expression (28,50) and to increase local cerebral glucose use (23) in the nucleus. Moreover, in the NTS, nicotinic acetylcholine receptors have been observed (26,47); neurons recorded in vitro after dissociation have been found to respond to bath applications of nicotine (49), and the existence of neurons activated in vivo by intravenous nicotine has been mentioned (58).

The main purpose of the present investigation was to study in vivo the neuronal responses to IV nicotine in the caudal NTS and to determine whether glycemia-sensitive neurons are preferentially affected. For some of the nicotine-responsive neurons, we also attempted to determine whether this kind of sensitivity involved a direct or indirect mechanism by comparing the responses to IV and local iontophoretic nicotine administrations. To determine whether the indirect response of NTS neurons to IV nicotine is due to activation of central vs. peripheral receptors, we observed the electrophysiological effects of nicotinic agonists and antagonists unable to cross the blood–brain barrier. The possible response of recorded neurons to vagal stimulation was also investigated. The possible adrenergic or noradrenergic nature of nicotine-responding neurons was assessed with a clonidine test routinely employed by other groups, who considered this α_2 adrenergic autoreceptor agonist to be a selective inhibitor of the central noradrenergic and adrenergic neurons based on its depressor effect on the cells in different noradrenergic and adrenergic nuclei (35,43).

METHOD

Animals and Operative Procedures

Experiments were performed on 60 adult male Sprague–Dawley rats weighing 350 ± 61 g (mean ± SD). Anesthesia was induced by intramuscular administration of 40 mg/100 g of ketamine hydrochloride (Imalgène 1000, Rhône-Mérieux) and maintained by continuous infusion of the anesthetic into the femoral vein (30 mg/ml; flow rate 3–13 μl/min). Ketamine has been reported to have only a minor effect on glycemia (3). Rectal temperature was monitored by a thermister and maintained between 36.5 and 37.5°C by means of an electrically heated blanket. A catheter was inserted into the left jugular vein to allow injection of NaCl, glucose, phlorizin, and nicotinic drugs.

Blood Glucose Level (BG) Monitoring

A Y-shaped silastic catheter was inserted into the right carotid artery to allow for the inward infusion of heparin solution (rate 1 μl/min) and the withdrawal of uncoagulated blood. BG was continuously monitored by passing blood at the rate of 15 μl/min through the sample chamber of a glucose analyzer (YSI, model 23A) (24). To avoid hemorrhagic stress, the total duration of blood withdrawal was kept below 2 h.

Hyperglycemia and hypoglycemia were induced by 4- and 10-min IV infusions, respectively, of glucose (20–30 mg in 0.2 ml) and phlorizin dihydrate (Aldrich; 0.35 mg in 0.1 ml saline/100 g). Control injections of NaCl with the same osmolarity were systematically performed.

Drug Administration

All systemically administered compounds were dissolved in saline. Doses of nicotine hydrogen tartrate (Sigma, St. Louis, MO, USA) were 30, 40, 60, and 80 μg/kg. Injected doses of the other nicotinic substances were in accordance with previous studies (7,15,34): tetramethylammonium (TMA, 0.1 mg/kg; Sigma), an agonist unable to cross the blood–brain barrier; chlorisondamine chloride (0.3 mg/kg; generously donated by CIBA-Geigy, Basle, Switzerland), an antagonist unable to cross the blood–brain barrier; and mecamylamine (0.5 mg/kg; Sigma), an antagonist that readily crosses the blood–brain barrier.

Vagus Nerve Stimulation

The left cervical vagus nerve was dissected away from the carotid artery for several millimeters and stimulated by means of a bipolar silver stimulating electrode that was tied in place around the nerve. The stimulation parameters were duration 0.5 ms, voltage 20–40 V, and frequency 0.1 Hz.

Microelectrophoresis

Microelectrophoretic applications with calibrated currents (Bionic Instrument SI 2101A and SI 2001A units) were performed using seven-barrel glass capillary pipettes (Clark, GC 150F) pulled in two stages with a Narishige PE-2 vertical puller and broken to a tip diameter of 14–18 μm. The central barrel and one outer barrel were filled with 0.2 M NaCl for current balancing and iontophoretic ejection of sodium, respectively. Three outer barrels were filled with glucose (0.5 or 1 M) and nicotine (0.5 M, pH = 3.5) dissolved in saline and with clonidine chloride (0.1 M, pH = 4; Sigma) dissolved in distilled water. Retaining currents were routinely used.

Single Unit Recording

The skull of the rat was fixed in a stereotaxic headholder according to Paxinos and Watson (39), and a limited area of the mediodorsal part of the interparietal bone over the cerebellum was exposed. Extracellular action potentials were recorded through a tungsten electrode (impedance 4–5 MΩ at 1,000 Hz), either single or glued at the multibarrel electrode (see above) and connected to a cathode-follower. Spikes were observed on an oscilloscope and selected by a window discriminator; frequency was measured, in some cases in parallel with BG, on a microcomputer (Apple II GS) using custom-designed software (6). Peristimulus histograms were also constructed with additional software to analyze the response to vagal nerve stimulation. Standard histogram parameters were 10 ms/bin analysis time for 100 bins (1-s sweep) and for 10–100 repetitions.

Statistical Analyses

Responses to local applications. Each neuron was tested with several electrophoretic applications of the same compound at increasing current intensities. Changes in neuronal firing frequencies were considered as responses if they were reproducible and dose-related.

Responses to systemic administrations. When computer graphs indicated that the basal firing rate changed by at least 15% after IV injection of a compound, Student's *t*-test (significance

level $p < 0.05$) was used to compare the mean discharge frequency during the period of modified activity with that of a control period of at least 10 min immediately preceding the administration.

The proportion of different responses observed in two neuronal populations was compared using a chi-square or Fisher test (significance level $p < 0.05$).

Histological Control Procedure

At the end of the experiment, the location of the recorded cell was marked by passing 8–9 μA of negative current for 8–10 s to create a small lesion around the tip of the electrode. The animals were intracardially perfused with 10% formalin, and the brain stem was removed and stored for at least 24 h in the same fixative solution. Serial coronal sections 15 μ thick were cut with a Vibratome and stained with cresyl violet.

RESULTS

Location of the Neuronal Recording Sites

Sixty units were recorded before, during, and after IV nicotine injection. All were located in the caudal part of the NTS, as confirmed by histological control (Fig. 1).

Neuronal Responses to IV Nicotine

Of the 60 recorded neurons, 44 changed their activity by 30 ± 21% (mean ± SD) after nicotine injection. The responses had a latency of 4 ± 3 min (mean ± SD), lasted 11 ± 8 min, and consisted of an increase in activity in 13 cells (Fig. 2) and a decrease in 31 others (Fig. 3A).

The mean basal firing rate of the recorded neurons was 27.47 ± 16.33 spikes/s. The mean basal firing rates of the neurons that were excited, depressed, or unaffected by IV nicotine were 22.86 ± 14.25, 28.89 ± 19.46, and 29.72 ± 7.67 spikes/s, respectively. The differences did not reach significance. No modulation in the firing of nicotine-responsive neurons by breathing or heart rate was observed.

Responses to IV Nicotine of Glycemia-sensitive and Non-glycemia-sensitive Neurons

The 60 neurons were also tested with moderate hyperglycemia (mean 15%), followed in 14 neurons by induced moderate hypoglycemia (mean 17%). Hyperglycemia induced a firing increase in 14 cells and a firing decrease in 16 others. The proportion of nicotine-responsive cells was significantly higher among the glycemia-sensitive neurons (41/43) than among the non-glycemia-sensitive ones (3/17) ($\chi^2 = 38.335, p < 0.001$, df = 1).

Of the 41 glycemia-sensitive neurons responding to IV nicotine, 15 were also tested with a local electro-osmotic ejection of glucose. All responded in the same direction to local and systemic glucose administrations.

Comparative Effects of IV Injection and Local Application of Nicotine

Twenty-three neurons were tested with both nicotine administrations. Local nicotine excited 4 of them, depressed 5 others, and failed to affect the firing of the 14 remaining neurons. Of the 23 neurons, 17 responded to either IV nicotine (8 cells) or local nicotine (2 cells) or both (7 cells). A comparison of the effects of both administrations on the same cells revealed that only four cells responded in the same direction to local and systemic nicotine (Fig. 3A, C). The four neurons also responded in the same direction to local and systemic glucose administrations (Fig. 3B).

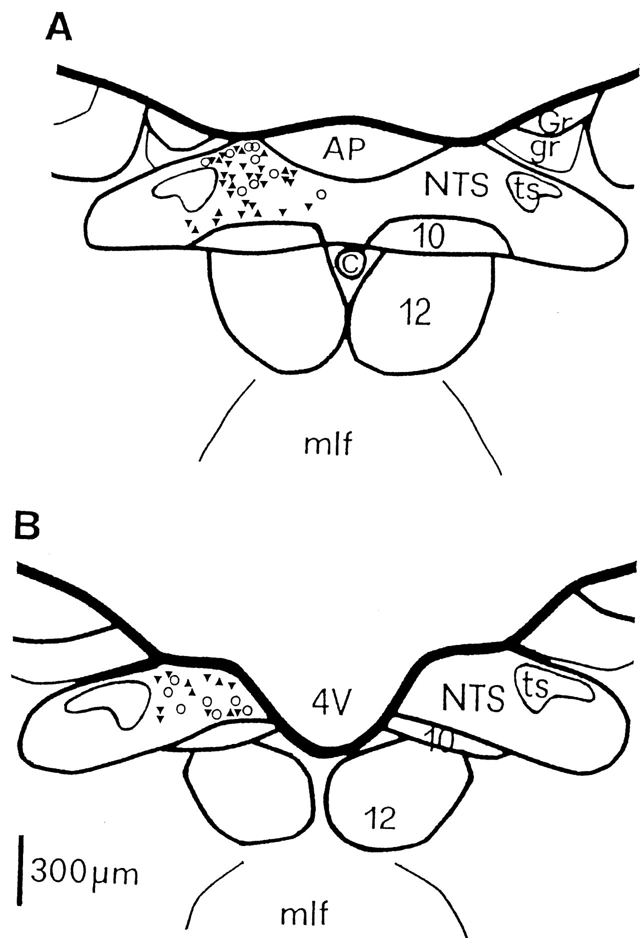

FIG. 1. Two coronal planes through the caudal NTS showing the location of 60 neurons that were activated (▲), depressed (▼), or unaffected (○) by IV nicotine injection. A. Area postrema level. B. Area immediately anterior to the area postrema. AP, area postrema; C, central canal; Gr, gracile nucleus; gr, gracile fasciculus; mlf, medial longitudinal fasciculus; NTS, nucleus tractus solitarius; ts, tractus solitarius; 4V, fourth ventricle; 10, motor nucleus of the vagus nerve; 12, nucleus of the hypoglossal nerve.

Comparative Effects of IV Injection of Nicotine and TMA

The peripheral vs. central origin of the sensitivity of 25 neurons to nicotine was investigated by comparing their response to IV nicotine and TMA. Seventeen of them responded in the same direction to systemic injection of the two compounds (Fig. 4), suggesting the involvement of peripheral nicotinic receptors. In the eight remaining cells, a discrepant response to TMA compared with that to nicotine suggested the involvement of central nicotinic receptors: five responded in the opposite direction to TMA and the other three were unaffected (Fig. 5).

Of the 25 neurons, 14 were recorded following stimulation of the ipsilateral vagus nerve. The spike frequency of 12 of the neurons either increased (10 neurons; Fig. 4B) or decreased (2 neurons), and the mean response latency was 12.5 ± 6.2

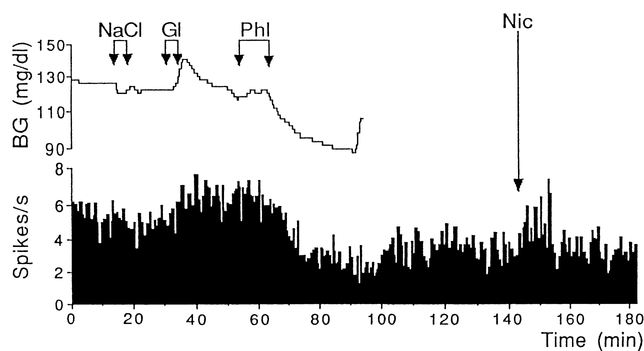

FIG. 2. Activity of an NTS glycemia-sensitive neuron recorded in parallel with the blood glucose level (BG). Unit response to IV nicotine injection. Activity was increased by induced hyperglycemia (Gl: IV glucose injection, 20 mg) and IV nicotine injection (Nic: 10.35 μg), depressed by induced hypoglycemia (Phl: IV phlorizin injection, 1.21 mg), and unaffected by a control injection of isotonic saline (NaCl).

ms. The proportion of responsive cells did not differ significantly between the neurons that responded in the same direction to nicotine and TMA (8/9) and the others (4/5) (Fisher test: $p = 0.6$).

Effects of Chlorisondamine on the Neuronal Responses to IV Nicotine

In 12 neurons, the peripheral or central origin of the sensitivity to nicotine suggested by the effect of TMA was further assessed by testing the possible effect of IV chlorisondamine on the response to IV nicotine. In all but two neurons, the effects of TMA and chlorisondamine were consistent with each other: a) in seven cells, which responded in the same direction to IV nicotine and TMA, the involvement of peripheral receptors was confirmed by the blocking effect of IV chlorisondamine on the response to IV nicotine (Fig. 4A); and b) in three others, which displayed discrepant responses to IV nicotine and TMA, the involvement of central receptors was strengthened, because the response to IV nicotine failed to be affected by IV chlorisondamine (Fig. 5).

Effect of Clonidine on Nicotine-responsive Cells

The effects of both clonidine iontophoresis and IV nicotine were tested on 25 neurons. All but one of the nicotine-responsive cells were depressed by local administration of clonidine (Fig. 3D), and a significantly greater number of nicotine-responsive than of nicotine-unresponsive neurons were depressed by clonidine (13/14 vs. 4/11; $\chi^2 = 6.625, p < 0.025$, df = 1).

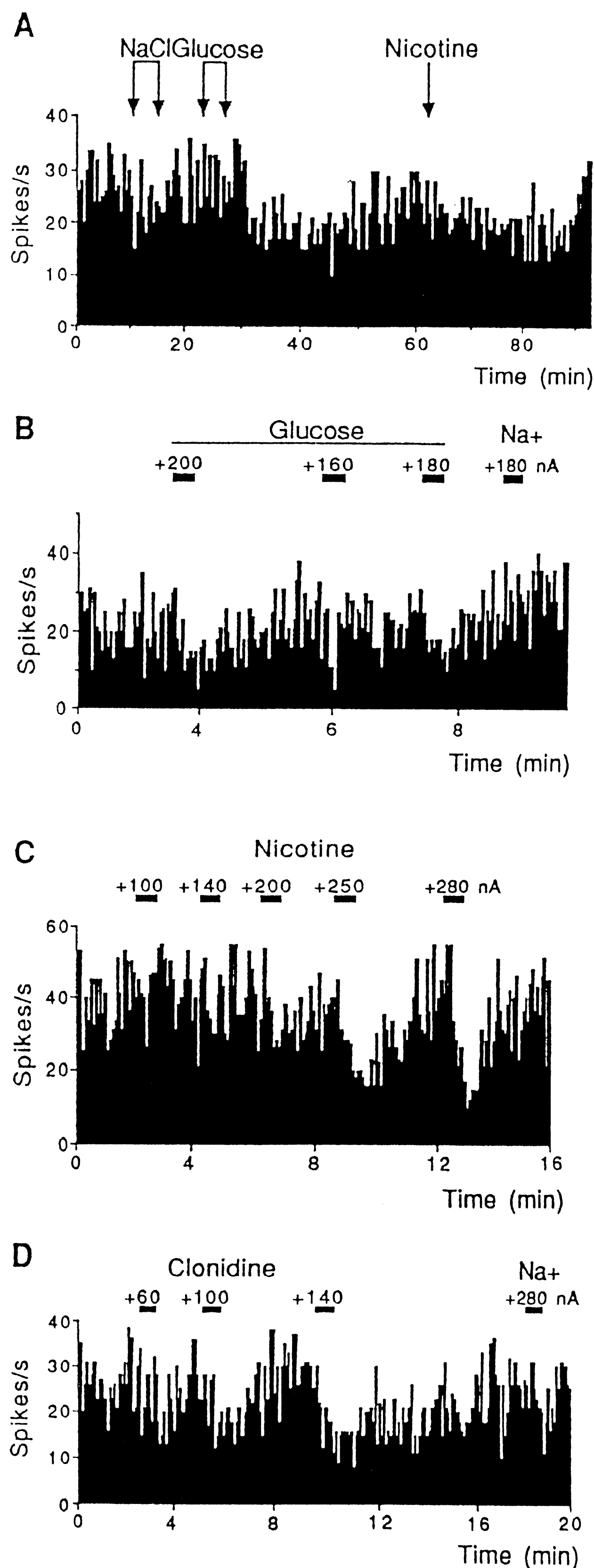

FIG. 3. Responses of an NTS glycemia-sensitive neuron to IV and local administrations of glucose and nicotine, and to local clonidine applications. A. Activity was depressed by glucose (20 mg) and nicotine (10.80 μg) IV injections and unaffected by control injection of isotonic saline (NaCl). B. Activity was dose-dependently depressed by local electro-osmotic application of glucose and unaffected by a control ejection of Na^+ ions. C. Activity was dose-dependently depressed by nicotine iontophoresis. D. Activity was dose-dependently depressed by clonidine iontophoresis and unaffected by a control ejection of Na^+ ions.

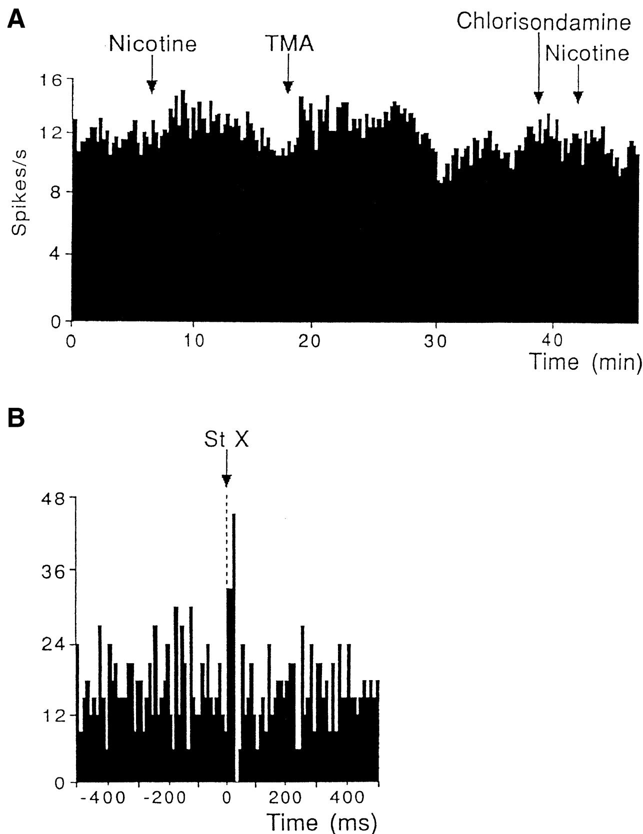

FIG. 4. Example of an NTS neuron responding to nicotine via peripheral receptors. A. Activity was increased by nicotine (8.55 μg) and the peripherally acting agonist tetramethylammonium (TMA, 0.03 mg). The response to nicotine was blocked by the peripherally acting antagonist chlorisondamine (0.08 mg). B. Peristimulus histogram showing excitatory response to vagal stimulations. The stimulus voltage was 30 V. Stimuli were delivered at 0 ms on the *x*-axis at a rate of 0.1 Hz with 17 repetitions.

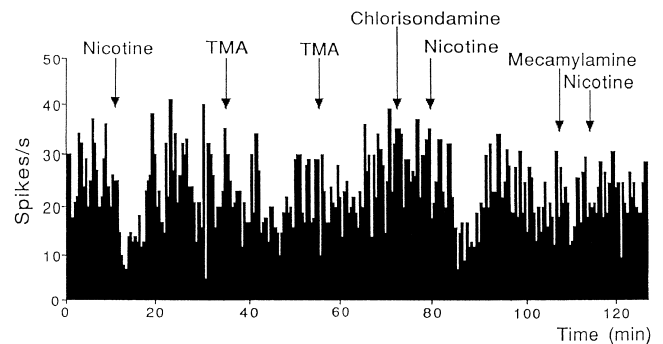

FIG. 5. Example of an NTS neuron responding to nicotine via central receptors. The activity was depressed by IV nicotine injection (8.85 μg), and the response was unaffected by the peripherally acting antagonist chlorisondamine (0.09 mg) but suppressed by the centrally acting antagonist mecamylamine (0.15 mg). The peripherally acting agonist tetramethylammonium (TMA, 0.03 mg) had no effect.

DISCUSSION

More than 70% of the neurons recorded in the caudal NTS responded to IV nicotine. For only one-fourth of them, which responded in the same direction to local application of the molecule, did sensitivity to systemic nicotine probably result from the action of a direct mechanism. Some of the direct responses consisted of a decrease in activity (Fig. 3C). This is unusual considering that nicotinic receptor activation induces an inwardly cationic current in dissociated NTS neurons (49). Thus, the inhibitory responses observed in our study could result from the excitation of inhibitory nicotinoceptive interneurons close to the recorded neuron. However, nicotinic receptor-mediated inhibition has been observed in neurosecretory cells of the paraventricular hypothalamic nuclei (36), in cerebellar Purkinje neurons (10), and in dorsolateral septal neurons (54). In the last case, membrane hyperpolarization resulted from a calcium-dependent increase in potassium conductance following selective activation of calcium conductance (54).

Conversely, most NTS cells sensitive to IV nicotine responded indirectly, i.e., through afferent nicotine-sensitive pathways that might originate either in the central nervous system or in the periphery. In the case of nicotine-responsive neurons that failed to respond to TMA, a central origin was likely (Fig. 5). The sensitivity of the neurons that responded to IV TMA in a manner resembling that of nicotine was assumed to depend on peripheral receptors. This possibility was reinforced for the cells whose response to nicotine was blocked by the peripherally acting antagonist chlorisondamine (Fig. 4A). For the two neurons that did not fulfill the second condition, a mixed response of central *and* peripheral origin cannot be excluded. A mixed origin might also be speculated for the neurons that responded in the opposite direction to nicotine and TMA, with a stronger central action masking the peripheral one. The indirect response to nicotine recorded in another hindbrain nucleus, the locus coeruleus, has been claimed to be caused by the activation of peripheral receptors located on C-afferent neurons (15). Similarly, one could contend that in the caudal NTS, the indirect nicotine responses of peripheral origin are due to vagal afferent neurons. Indeed, functional nicotinic receptors are expressed in the nodose ganglion (16,27), mainly on type C neuronal somata (16). This hypothesis is in line with the response of most recorded neurons to vagal stimuli. The fact that many of these cells responded to nicotine by a decrease in activity suggests that they are connected to vagal afferents by inhibitory interneurons. The hypothesis is also consistent with the probable adrenergic or noradrenergic nature of nicotine-responsive neurons, supported by their depressed firing after clonidine, considering that many vagal afferents synapse with tyrosine hydroxylase immunoreactive dendrites in the caudal NTS (46).

NTS responses to nicotine might also be due to side effects such as a drop in blood pressure induced by the drug. Although blood pressure was not routinely monitored in our experiment, we consider this hypothesis as hardly compatible with the selective effect of nicotine on glycemia-sensitive neurons. Indeed, most glycemia-sensitive neurons recorded in the caudal NTS responded to IV nicotine. Because their sensitivity to glycemic changes within the physiological range is compatible with their involvement in nutritional regulation, these neurons might mediate some of the nutritional effects of nicotine, resulting in a decrease in weight gain, as hypothesized in the introduction. Clonidine depressed almost all nicotine-responsive neurons and did not affect a majority of the other neurons recorded in that area. Insofar as this inhibitory response to clonidine reflects adrenergic or noradrenergic iden-

tity, the relevant neurons might contribute to the disturbing influence exerted by nicotine on nutritional function through catecholaminergic signals sent to the lateral hypothalamic area and the paraventricular hypothalamic nucleus; catecholaminergic inputs to these nuclei modulate feeding behavior (20,21) and originate partly in the caudal NTS (8,9,42). Neurons sensitive to IV nicotine have also been found in the lateral hypothalamic area (18), and it is worth noting that in both structures, the proportion of cells responsive to nicotine is significantly higher among glycemia-sensitive than among non-glycemia-sensitive cells. This comparison suggests that a glycemia-sensitive system comprising these two structures is influenced by systemic nicotine.

Apart from their putative role in nutritional function, the nicotine-responsive NTS neurons may also be involved in cardiovascular or respiratory regulation or in neuroendocrine control. On the one hand, local injection of nicotine in the caudal NTS decreases blood pressure and heart rate (48), and neurons in the caudal NTS are activated by inhalation of cigarette smoke through vagal pulmonary receptors (58). However, the nicotine-sensitive neurons recorded in the present study were not related to heart rate or to breathing. On the other hand, catecholamines released in the hypothalamic paraventricular nucleus after injection of nicotine in the fourth ventricle (30) stimulate the secretion of prolactin (31) and adrenocorticotropic hormone (32), and the adrenergic and noradrenergic cell groups in the NTS are probably involved in the effect (29).

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