Nicotine Impairs Reflex Renal Nerve and Respiratory Activity in Deoxycorticosterone Acetate–Salt Rats

Shirley A. Whitescarver, Andrew M. Roberts, Richard W. Stremel, Agnes E. Jimenez, and John C. Passmore

Smoking exacerbates the increase in arterial pressure in hypertension. The effect of nicotine on the baroreceptor-mediated reflex responses of renal nerve activity (RNA), heart rate, and respiratory activity (minute diaphragmatic activity [MDA]) after bolus injections of phenylephrine was compared in deoxycorticosterone acetate (DOCA)–salt sensitive and normotensive rats. Osmotic minipumps that dispensed either nicotine (2.4 mg/kg/day) or saline were implanted in DOCA and normotensive rats for 18 days. Anesthetized DOCA-nicotine, DOCA-saline, control-nicotine, and control-saline rats had mean arterial pressures (MAP) of 117±3, 110±9, 90±3, and 89±5 mm Hg, respectively. Nicotine decreased the sensitivity (p<0.05) of baroreceptor reflex control of RNA (%ΔRNA/ΔMAP) in the DOCA-nicotine rats (−0.92 ±0.08) compared with the DOCA-saline (−1.44±0.16), control-nicotine (−1.45±0.08), or control-saline (−1.45±0.21) rats. The reflex decrease in respiratory activity (%ΔMDA/ΔMAP × 100) was impaired (p<0.01) in both control-nicotine (−24.5±3.3) and DOCA-nicotine (−18.2±4.6) rats compared with control-saline (−59.2±9.1) and DOCA-saline (−52.5±9.9) rats. The reflex decrease in heart rate (absolute ΔHR/ΔMAP) in both DOCA-nicotine (1.56±0.17) and control-nicotine (1.54±0.24) rats was augmented compared with DOCA-saline and control-saline rats (0.91±0.12 and 0.97±0.14). Thus, chronic nicotine impairs reflex control of RNA in response to increases in arterial pressure only in DOCA-salt hypertensive rats, whereas nicotine impairs reflex respiratory activity and augments the reflex decrease in heart rate in normotensive and hypertensive rats. (Hypertension 1991;17:179–186)

Smoking causes an exaggerated and sustained increase in arterial pressure in hypertensive individuals1,2 in contrast to normotensive subjects who have only a transient increase in arterial pressure.3 Because nicotine elicits cardiovascular responses similar to those caused by smoking, nicotine is believed to be the ingredient in cigarettes that causes the further elevation of pressure in a hypertensive subject who smokes.4 Spontaneously hypertensive rats5 and genetically hypertensive mice6 also have an increased pressor response to nicotine compared with their normotensive controls. However, in either normotensive dogs7 or rats,8 chronic administration of nicotine is reported to have minimal effects on arterial pressure.

Although the specific mechanisms for the exaggerated increase in arterial pressure in hypertensive humans or animals given nicotine is unknown, evidence suggests an interaction of nicotine with the central nervous system. In animals, nicotine stimulates central sympathetic outflow,9,10 increases catecholamine secretion at sympathetic ganglia,11,12 increases vasopressin release13-14,13 increases release of adrenomedullary epinephrine,15 and stimulates carotid body chemoreceptors.16 Thus, nicotine causes a general sympathetic adrenergic stimulation of the cardiovascular system that may interact with the pathological alteration in sympathetic neural control already present with hypertension.

Recently, Passmore and Jimenez17 found that chronic nicotine infusion augmented the increase in arterial pressure of rats given deoxycorticosterone acetate (DOCA) and a high salt diet (DOCA-salt hypertension). In contrast, the arterial pressures of normotensive rats given nicotine were not significantly different from controls. Because nicotine ex-
acerbates the development of hypertension in DOCA-salt hypertensive rats\(^1\) and an enhanced efferent renal nerve activity is necessary for the full development of DOCA-salt hypertension.\(^1\)\(^8\) our objective was to determine if baroreceptor reflex-mediated decreases in renal nerve activity in response to increases in arterial pressure were impaired in DOCA-salt rats treated with nicotine. Transient increases in arterial pressure also inhibit respiration and heart rate through the carotid and aortic baroreceptor reflex.\(^1\)\(^9\) To determine if nicotine affects these other baroreceptor reflex-mediated responses, we compared the degree of respiratory suppression and other baroreceptor reflex-mediated responses, we compared the degree of respiratory suppression and the decrease in heart rate in response to vasopressor-induced transient increases in arterial pressure in nicotine- and saline-treated normotensive and DOCA-salt hypertensive rats.

**Methods**

**Preparation of Animals**

Male Sprague-Dawley rats (75–100 g) were housed individually in light- and temperature-controlled rooms and were randomly assigned to either control or DOCA-treated groups. DOCA-treated rats were anesthetized with methoxyflurane and then uninephrectomized. Twelve days were allowed for recovery from surgery and hypertrophy of the remaining kidney; then DOCA pellets (75 mg) were implanted subcutaneously. Fresh pellets were implanted every 2.5 weeks.

All rats were fed a high salt diet containing 1.1 meq Na\(^+\) and 0.75 meq Cl\(^-\) per gram of diet. To counteract potassium wasting in the DOCA-treated group, 0.65 meq K\(^+\) per gram of diet was added to the high NaCl chow. Preparation of these diets has been described previously.\(^2\)\(^0\)

After 2 weeks on the high salt diet, the control and DOCA-treated groups of rats were each divided into nicotine and non-nicotine (saline)-treated groups. In nicotine-treated rats, nicotine (titrated to a pH of 7.4) was infused into the subdermal tissues by osmotic minipumps (Alzet model 2ML4; Alza Corp., Palo Alto, Calif.) at a rate that delivered 2.4 mg/kg/day nicotine. We have shown (unpublished data from our laboratory) that this amount of nicotine results in an average blood nicotine level of 82±9 ng/ml (equivalent to 2 packs cigarettes/day). For saline-treated rats, saline was infused instead of nicotine. Therefore, four groups of rats were studied: DOCA-nicotine (n=9), DOCA-saline (n=6), control-nicotine (n=7), and control-saline (n=6).

Systolic tail-cuff pressures (Narco Bio-Systems Inc., Houston, Tex.) were measured twice weekly. Baroreceptor reflex control of renal nerve activity, heart rate, and respiratory activity were studied 18±1 days after implanting the osmotic minipumps. Passmore and Jimenez\(^1\)\(^7\) have shown that nicotine produces a significant exacerbation of the hypertension within this time period.

Rats were anesthetized with a mixture of \(\alpha\)-chloralose and urethane (60 mg/kg and 750 mg/kg, respectively, i.p.). The trachea was cannulated and the rats were allowed to breathe spontaneously. The left femoral artery was cannulated to record arterial pressure with a pressure transducer (model P23db, Statham Laboratories, Inc., Hato Rey, Puerto Rico). Heart rate was recorded using a tachograph (model 7P4H, Grass Instrument Co., Quincy, Mass.) triggered from the arterial pressure pulse, and a catheter was placed in the right jugular vein for infusion of drugs. All physiological variables were recorded by a polygraph (model 7, Grass).

**Renal Nerve Activity**

The left kidney was exposed through a retroperitoneal flank incision. With use of a dissecting microscope, a branch of the renal nerve running along the renal artery was carefully isolated and cleared of connective tissue. Renal nerve activity was recorded by a bipolar platinum electrode connected to a high impedance probe (Grass). Neural signals were amplified (20,000–50,000×) and filtered (30–3,000 Hz) by a bandpass amplifier (model P511, Grass). The signal was monitored with a loudspeaker, displayed on a digital storage oscilloscope (Gould 1425, Hainault, Essex, England) and integrated (P10F cumulative integrator, Grass). A window discriminator (Frederick Haer and Co., Brunswick, Mass.) was used to minimize noise and emphasize changes in neural activity and the output integrated (P10F, Grass). The renal nerve was crushed at the end of the experiment, and any residual signal (noise) was subtracted when nerve activity was calculated. Nerve activity was expressed as the percent change from control for each response. Changes in nerve activity measured by the two methods agreed well. For calculations involving renal nerve activity, we used the integrated output of the window discriminator.

**Respiratory Activity**

Diaphragmatic electromyographic (DEMg) activity was recorded to monitor respiratory activity. Two Teflon-coated stainless steel wires (0.003 mm in diameter) with the ends (2–3 mm) stripped of insulation and bent as hooks were placed in the diaphragm by a 22 gauge needle. The raw DEMg signal was amplified (P511, Grass) and integrated (7P3C running average integrator, Grass). Because the peak amplitude of the integrated DEMg is correlated with tidal volume,\(^2\)\(^1\) the diaphragmatic motor equivalent of minute ventilation (minute diaphragmatic activity [MDA]) was calculated as breathing frequency times peak-integrated DEMg.

**Protocol**

Arterial pressure was increased by intravenous bolus doses of phenylephrine (0.25–2.00 \(\mu\)g/kg). The peak pressor responses and their associated peak
reflex changes were recorded for each dose. The drugs were injected in bolus doses of less than 20 μl, and at least 5 minutes were allowed between doses. Changes in renal nerve activity, heart rate, and DEMG activity in response to the increases in arterial blood pressure were recorded.

**Data Analysis**

Mean arterial blood pressure and renal nerve activity were measured before and during the peak increases in arterial pressure caused by phenylephrine. The peak change in renal nerve activity was measured over a 5-second interval. Changes in mean arterial pressure (mm Hg) and changes in renal nerve activity (percent change from control) were plotted. Using a least-squares analysis, a straight line was fitted through the linear portion of the curve for each rat. The slope of this line was used as an index of baroreceptor reflex sensitivity.

Heart rate responses to increases in arterial blood pressure between 40 and 60 mm Hg were compared among groups of rats. Because the heart rate responses in anesthetized rats are attenuated compared with conscious rats, a baroreceptor reflex sensitivity curve was not generated. The reflex decrease in heart rate was determined from the mean of two to three doses of phenylephrine per animal. The ratio of the absolute change in heart rate (beats/min) and change in mean arterial pressure (mm Hg) were used to determine the reflex gain of the heart rate reflex.

To quantitate respiratory responses to acute increases in arterial blood pressure, MDA (frequency×DEMG) was determined before and during the peak pressure changes induced by bolus injections of phenylephrine. Large pressure challenges between 40 and 60 mm Hg obtained early in the experiment were used. These respiratory responses were normalized for the magnitude of the blood pressure change by dividing the percentage change in MDA by the increase in arterial pressure (mm Hg). The product was multiplied by 100 and the respiratory sensitivities were compared among the four groups.

A one-way analysis of variance was used to compare baroreceptor reflex sensitivity of renal nerve activity, reflexly induced respiratory and heart rate responses, and mean arterial pressure among groups. A three-way analysis of variance with repeated measures was used to analyze systolic tail-cuff pressures over the 4-week period. Duncan’s multiple range test was used to determine statistical significance with \( p<0.05 \) considered significant.

**Results**

**Arterial Pressure**

Systolic tail-cuff pressures were not different among the four groups of rats before the DOCA-salt protocol (week 0, Figure 1). After 2 weeks of DOCA and a high salt diet, systolic blood pressures of DOCA-nicotine rats were significantly \( (p<0.01) \) increased compared with the non-DOCA-treated rats. Systolic pressures in the non-DOCA-treated rats (control-nicotine and control-saline) were unaltered by the high salt diet throughout the study.

After 1 week of nicotine infusion, DOCA-nicotine rats had systolic tail-cuff pressures that were higher \( (p<0.05) \) than DOCA-saline rats (week 3, Figure 1). However, after 2 weeks of infusions (week 4), tail-cuff pressures were not significantly different between the DOCA-nicotine \( (142±5 \text{ mm Hg}) \) and DOCA-saline \( (133±8) \) rats. The systolic tail-cuff pressures in both the DOCA-nicotine and DOCA-saline rats were higher \( (p<0.01 \text{ and } p<0.05, \text{ respectively}) \) than pressures of either control-nicotine or control-saline rats. Tail-cuff pressures of control-nicotine and control-saline rats were not significantly different from each other at any time after initiation of nicotine treatment.

Direct mean arterial pressures of anesthetized DOCA-nicotine rats, although higher on the average, were not significantly different from the pressures of DOCA-saline rats (Table 1). Arterial pressures of

![FIGURE 1. Line graph showing systolic tail-cuff pressures in the four groups of rats fed a high salt diet. At week 0, half the rats were treated with deoxycorticosterone acetate (DOCA). At week 2, nicotine or saline osmotic minipumps were implanted. *\( p<0.05 \) compared with DOCA-saline rats. †\( p<0.05 \) and ††\( p<0.01 \) compared with control-nicotine or control-saline rats.](http://hyper.ahajournals.org/)

<table>
<thead>
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<th>Group</th>
<th>MAP (mm Hg)</th>
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<td></td>
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<tr>
<td>Nicotine</td>
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<td>Saline</td>
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Values are mean±SEM. MAP, mean arterial pressure; HR, heart rate.

*\( p<0.01 \) and †\( p<0.05 \) compared with control-nicotine and control-saline rats.
the DOCA-nicotine and DOCA-saline rats were greater (p<0.01 and p<0.05, respectively) than either the control-nicotine or control-saline rats. Resting heart rates were not different among the four groups of rats (Table 1).

Renal Nerve Activity

Decreases in renal nerve activity caused by increasing arterial pressure were impaired after 18 days of nicotine in the DOCA rats (Figure 2). Although mean arterial pressures of anesthetized DOCA-nicotine and DOCA-saline rats were not significantly different (Table 1), the calculated baroreceptor reflex sensitivity of renal nerve activity was significantly (p<0.05) less in the DOCA-nicotine group compared with the DOCA-saline group (Figure 3). In contrast, control-nicotine rats had no alteration in baroreceptor reflex sensitivity of renal nerve activity compared with control-saline rats.

Heart Rate

In contrast to renal nerve activity, the reflex decrease in heart rate was greater (p<0.05) in rats infused with nicotine compared with those infused with saline (Figure 4). The reflex gain (absolute change in heart rate divided by the increase in arterial pressure) was 1.7 times greater in the DOCA-nicotine rats compared with the DOCA-saline rats. The mean reflex gain of the control-nicotine rats was 1.6 times greater than the gain in the control-saline rats. There was no difference between the two saline- or the two nicotine-treated groups.

Respiratory Activity

The reflex decrease in respiratory activity (MDA) caused by increasing arterial pressure was reduced (p<0.01) in both groups of rats treated with nicotine (Figure 5). The sensitivity or reflex gain (percent...
change in MDA divided by the increase in arterial pressure (times 100) of this inhibitory reflex in DOCA-nicotine rats was only 32% of that found in the DOCA-saline rats. Similarly, the control-nicotine rats had only 41% of the reflex sensitivity of the control-saline rats. There were no significant differences in the sensitivity of the reflex between the two groups of saline or between the two groups of nicotine-treated rats. Although baseline respiratory frequencies tended to be higher in nicotine-treated animals, there were no significant differences among the four groups of rats.

**Discussion**

Our results show that nicotine impairs the baroreceptor reflex control of renal nerve activity at an early stage in the development of DOCA-salt hypertension. In contrast, 18 days of nicotine infusion did not alter baroreceptor reflex control of renal nerve activity in the non-DOCA-treated, normotensive rats. In addition, we found that chronic nicotine augmented the reflex decrease in heart rate and impaired the reflex decrease in respiratory activity in response to acute increases in arterial pressure in normotensive as well as in hypertensive rats. Thus, nicotine has diverse effects on reflexly mediated cardiovascular and respiratory responses.

In our study, 7 days of nicotine infusion increased systolic tail-cuff pressures in DOCA-treated rats but did not alter tail-cuff pressures of normotensive, non-DOCA-treated rats. Two weeks after implantation of the osmotic minipumps, systolic tail-cuff pressures in awake animals and direct mean arterial pressures in anesthetized animals tended to be greater but were not significantly elevated in the DOCA-nicotine rats compared with the DOCA-saline rats. Pooling of data from several experiments (J.C. Passmore, unpublished data) shows that with greater than 25 animals per group, there is a significant exacerbation of DOCA-salt hypertension for weeks 1 through 3 after nicotine treatment. The lack of a significant difference in the present study may be due to the smaller number of animals and the greater variability in the tail-cuff and direct arterial pressures measured in the DOCA-saline rats at week 4. Our results and those of Passmore and Jimenez are consistent with studies in humans that have found that hypertensive individuals have an exaggerated and sustained increase in arterial pressure with chronic exposure to nicotine.

Similar to our study, Wenzel et al and Wenzel and Azmez found that chronic treatment with nicotine increased arterial pressure in hypertensive rats. However, they reported a biphasic effect of nicotine on arterial pressure in normotensive rats as well as two-kidney, one clip hypertensive rats. This biphasic effect of nicotine in hypertensive rats consisted of an increase in arterial pressure during the first few weeks of hypertension followed by an attenuation of the hypertension after 15 weeks. In the current study and in the original study by Passmore and Jimenez, normotensive rats given nicotine showed no difference in systolic tail-cuff pressures compared with saline-infused normotensive rats. Our results are consistent with studies in normotensive dogs and rats in which chronic nicotine treatment had minimal effects on arterial pressure.

Alterations in centrally mediated sympathetic neural control have been reported in DOCA-salt rats prior to a significant elevation in arterial pressure. In addition, an enhanced effenter renal nerve activity is necessary for the full development of DOCA-salt hypertension. Because nicotine exacerbates the development of hypertension in DOCA-salt rats, the first purpose of our study was to determine if baroreceptor reflex-mediated decreases in renal nerve activity were impaired by chronic nicotine infusion. We examined the effect of nicotine during the developmental stage of hypertension to minimize the contribution of chronic resetting of the arterial baroreceptors.

We found that baroreceptor reflex sensitivity of renal nerve activity was impaired in the DOCA-salt rats treated with nicotine. Although direct mean arterial pressures in anesthetized rats and indirect systolic tail-cuff pressures in awake animals were not significantly different between the DOCA-nicotine and DOCA-saline rats after 2 weeks of infusions, the systolic tail-cuff pressures after 1 week of nicotine treatment were significantly higher in the nicotine-treated DOCA rats compared with the saline-treated DOCA rats. Therefore, we cannot exclude the possibility of a pressure-induced chronic resetting of the arterial baroreceptors at this early stage of hypertension. However, other indices of baroreceptor resetting, attenuated reflex respiratory and heart rate responses, were not present. In our study, there were no differences in the reflex respiratory or heart rate responses between the saline-infused hypertensive (DOCA-saline) and normotensive (control-saline) animals or between the hypertensive (DOCA-nicotine) and normotensive (control-nicotine)
animals infused with nicotine. The lack of difference among the above groups suggests that the arterial baroreceptors were not yet reset in the hypertensive rats.

Although acute infusion of nicotine increases vascular resistance in the rat and dog, chronic exposure to cigarette smoke has produced variable alterations of vascular resistance in the rat. Barron et al. found a decrease in iliac vascular resistance in resting, normotensive rats exposed to cigarette smoke. In contrast, Bennett and Richardson found no alteration of resting iliac vascular resistance in normotensive rats exposed to cigarette smoke. However, when carotid sinus pressure was selectively increased or decreased, there were significantly larger adjustments in lower body vascular resistance (calculated from iliac blood flow) in the rats exposed to cigarette smoke. These results indicated that the sensitivity of the arterial baroreceptor reflex control of vascular resistance was greater in normotensive rats after exposure to smoke. Furthermore, when rats were subjected to a head-up tilt influencing both cardiopulmonary and arterial baroreceptors, there was a smaller decrease in peripheral vascular resistance (i.e., an increased sensitivity) in the rats exposed to smoke.

Although Bennett and Richardson found an increased sensitivity in reflexly induced sympathetic vascular resistance in normotensive rats exposed to cigarette smoke, we found no alteration of reflex sympathetic renal nerve activity in normotensive rats chronically infused with nicotine. The dissimilarity of results may be due to differences in protocol between the two studies. In their study, rats were exposed to cigarette smoke for 6–8 months, whereas our rats received an infusion of pure nicotine for only 18 days. In addition, the nature of the challenges in the two studies differed in that head-up tilt involves a decrease in arterial pressure, whereas our vasopressor infusions induced an increase in arterial pressure. Furthermore, selective alterations of carotid sinus pressure, as in the study by Bennett and Richardson, involve only the carotid baroreceptors, whereas our increases in arterial pressure affected both arterial and cardiopulmonary pressure receptors. The only nicotine-induced alteration of reflex sympathetic nerve activity found in our study was an impairment of reflex decreases in renal nerve activity in the DOCA-salt hypertensive rats.

Reflex decreases in heart rate in response to transient increases in arterial pressure were significantly enhanced by chronic nicotine treatment in both DOCA-salt and control rats. An increased gain in the baroreceptor-mediated heart rate reflex of normotensive rats chronically exposed to smoke was also reported by Bennett and Richardson. Rats subjected to tobacco smoke for 6–8 months had significantly greater reductions in heart rate in response to phenylephrine than sham-treated rats. The reflex gain in the rats exposed to smoke was 1.5 times that found in the sham-treated rats. In our study, rats infused with nicotine (DOCA-nicotine and control-nicotine groups) had a reflex gain of 1.6–1.7 times that found in rats infused with saline. Thus, both studies indicate that nicotine (or cigarette smoke), independent of the blood pressure status of the animal, increases the gain of the heart rate reflex.

Nicotine may influence heart rate through an effect on the peripheral chemoreceptors, arterial baroreceptors, or ganglionic transmission. Comroe and Mortimer found that acute stimulation of carotid chemoreceptors by nicotine causes bradycardia, whereas stimulation of aortic chemoreceptors by nicotine causes tachycardia. However, in our study and others, there were no differences in resting heart rates between chronic nicotine- and saline-treated animals.

Although chemoreceptor-mediated effects on heart rate elicited by nicotine are variable, Diamond has shown that local application of nicotine to the isolated carotid sinus of a cat increases the firing of the afferent nerves from the carotid sinus. The increase in the heart rate reflex could also be due to a facilitation of ganglionic transmission by nicotine. Gebber has demonstrated that low doses of nicotine facilitate ganglionic transmission and thus enhance the responsiveness of ganglia to centrally induced activity. The direct stimulatory action of nicotine on the carotid baroreceptors and ganglia might account for the increased gain of the heart rate reflex found in both groups of rats treated with nicotine in our study. However, such peripheral effects of nicotine cannot totally account for our findings since the reflex renal nerve activity was blunted only in the DOCA-salt hypertensive rats.

Finally, the decrease in heart rate caused by transiently increasing arterial pressure with bolus injections of phenylephrine is predominantly mediated by increased parasympathetic activity. Because the gain of the heart rate reflex was increased in both DOCA-salt and normotensive rats treated with nicotine, the increased gain could be due to a central action of nicotine on the parasympathetic portion of the reflex. In fact, microinjection of nicotine near the area postrema has been shown to cause bradycardia due to an increase in vagal tone.

In addition to the decreased heart rate associated with acute increases in arterial pressure, a decrease in MDA also occurs. This response is the result of activation of baroreceptor afferents from the carotid sinus. In the present study, chronic nicotine treatment significantly decreased the respiratory suppression associated with increases in arterial pressure in both control and DOCA-salt hypertensive rats. The direct effect of nicotine on aortic and carotid chemoreceptors is hyperpnea; however, baseline respiratory frequencies were not significantly different between nicotine- and saline-infused rats.

Other possible sites of action for nicotine that might alter respiration include enhancement of neuromuscular transmission via nicotinic receptors and stimulation of pulmonary afferents. Motor end-
plates on muscles such as the diaphragm would be stimulated by nicotine, thus causing an increase in the response to centrally induced activity. Because we observed an impairment in the reflex response to increased arterial pressure, this does not appear to be the mechanism of the impaired respiratory response. Ginzel et al. has shown that nicotine stimulates pulmonary afferents that project to respiratory centers in the brain. Stimulation of pulmonary afferents may alter neural output to the periphery. Thus, the impairment in respiration due to nicotine that we observed in both normotensive and hypertensive rats suggests a direct central effect of nicotine.

The diversity of the respiratory, heart rate, and renal nerve reflex responses we observed also suggests a central effect of nicotine. Although no measurements of central activity were made in this study, it is known that nicotine readily crosses the blood-brain barrier and is distributed throughout the brain. This drug has been shown to exert an effect on the cardiovascular system through nicotinic receptors in the dorsal and ventrolateral medulla and the nucleus tractus solitarius. For example, when nicotine is injected into the ventrolateral medulla, direct recordings from the greater splanchnic nerves indicate that it stimulates sympathetic neural output.

DOCA-salt hypertension is also associated with a centrally mediated increase in overall sympathetic tone and renal sympathetic nerve activity. Katholi et al. demonstrated the importance of increased renal nerve activity in the development of hypertension in DOCA-salt rats. In their study, renal denervation delayed the onset and attenuated the severity of hypertension by decreasing sodium retention. In our study, DOCA-salt hypertensive rats given nicotine had an impaired ability to decrease renal nerve activity in response to elevations in arterial pressure. This increase in sympathetic tone may further enhance sodium retention in the DOCA-salt rat and thus potentiate the development of hypertension in this salt-sensitive model of hypertension.

In conclusion, chronic nicotine exposure, the equivalent of a two-pack-a-day smoker, alters the physiological responses to vasopressor-induced increases in arterial pressure in both normotensive and DOCA-salt hypertensive rats. In DOCA-salt hypertensive rats, exposure to nicotine decreases the sensitivity of the baroreceptor reflex-mediated decrease in renal sympathetic nerve activity. In addition, chronic exposure to nicotine, independent of hypertension, decreases the gain of the respiratory response and increases the gain of the heart rate response to acute increases in pressure. The diversity of these reflex responses to an increase in pressure suggests a centrally mediated effect of nicotine.

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