Effects of nicotine and dietary salt on a learned blood pressure response in Dahl-S rats

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Kuo, Justin H., Richard O. Speakman, Aletia G. Sprinkle, Sheng-Gang Li, David R. Brown, and David C. Randall. Effects of nicotine and dietary salt on a learned blood pressure response in Dahl-S rats. Am J Physiol Heart Circ Physiol 284: H1793–H1799, 2003. First published January 9, 2003; 10.1152/ajpheart.00767.2002.—We examined the effects of chronic nicotine exposure and dietary salt on the arterial blood pressure (BP) changes learned in response to an acute behavioral stress in the Dahl salt-sensitive rat. Four groups were tested: low salt + vehicle; low salt + nicotine; high salt + vehicle; and high salt + nicotine. Rats were fed a low-salt (0.08% NaCl) or a high-salt (8% NaCl) diet for 4 wk; 2.4 mg·kg−1·day−1 nicotine or vehicle was given via an implanted osmotic minipump for the last 2 wk. All rats were conditioned by following one tone (CS+) with a 0.5-s tail shock; another tone (CS−) was never followed by shock. CS+ in low salt + vehicle and high salt + vehicle-treated rats evoked an initial arterial BP increase (C1), a component of the startle response, and an ensuing, smaller, but more sustained, pressor response (C2), which is acquired with training. In these rats, both C1 and C2 evoked by CS− were significantly smaller than those to CS+, demonstrating that these groups discriminated between the two tests. Conversely, although the low salt + nicotine-treated rats had both the C1 and C2 components of the conditional arterial pressure response, they did not discriminate between CS+ and CS−. Finally, the high salt + nicotine group failed to both discriminate between tones and acquire (i.e., learn) the C2 response. The unconditional response to shock did not differ between groups. We conclude that combined exposure to high salt and to nicotine inhibits the salt-sensitive animal’s acquisition of a learned conditional BP response, perhaps because nicotine acts preferentially on those central processes required for associative learning versus those involved in orientating to external stimuli.

Pavlovian conditioning; learning; stress; tobacco smoking; hypertension; autonomic nervous system

IT IS WIDELY ACCEPTED that “lifestyle” choices, particularly including nicotine exposure and behavioral stress, markedly influence arterial blood pressure (BP). In addition, a number of genes have been identified that appear to contribute to the etiology of hypertension by altering renal sodium reabsorption (e.g., 9), and, in fact, consumption of high levels of dietary salt is among those behaviors thought to figure in the cardiovascular health of the general population (1, 17, 26). The effect(s) of each of these factors on arterial BP is of physiological, clinical, and potentially societal importance. Therefore, the goal of the present experiment is to quantify the effects of chronic nicotine exposure and dietary salt in Dahl salt-sensitive (Dahl-S) versus salt-resistant rats upon a learned arterial BP response evoked by an acute behavioral stress.

We have used classical (i.e., Pavlovian) conditioning in rats to study arterial BP control. More specifically, presentation of a 15-s pulsed tone (i.e., the conditional stimulus or CS+) followed by a 0.5-s tail shock to an animal trained in the paradigm evokes a short latency, transient BP increase. We denoted this as the first component (C1) of the conditional response. C1 is followed by a lower amplitude pressor response, C2, which is sustained until delivery of the shock. C1 and C2 are of both behavioral and physiological interest. C1 is part of an unlearned startle (or orienting) response, although it is also capable of being modified by training (25). That is, presentation of a nonpulsed tone (i.e., CS−) of the same audio frequency as CS+ also elicits an initial pressor response analogous to C1, but, as the animal learns the behavioral paradigm, the amplitude of C1 becomes significantly smaller in response to CS− versus CS+. CS− does not evoke a BP increase analogous to C2. C2, therefore, is particularly characteristic of the learned conditional arterial BP response. Consequently, both the first and second components of the conditional BP response allow one to demonstrate that subjects discriminate between the reinforced and nonreinforced stimuli. In the particular context of the present experiment, we showed previously (3) that placing the “borderline hypertensive rat” on a high-salt (i.e., 8%) diet significantly alters the arterial BP conditional response pattern, as well as the change in BP evoked by a given change in sympathetic nerve activity (SNA).

We now report that nicotine exposure alone inhibits the ability of the rat to discriminate between CS+ and...
CS−, and that nicotine in combination with a high-salt diet markedly attenuates C2, the “hallmark” of the learned conditional arterial BP response. Preliminary reports of these experiments have been published (5, 12, 27).

METHODS

Subjects. Seventy-nine Dahl-S rats (Rapp strain, Harlan Industries; Indianapolis, IN) were used, and the rats were ≥3 mo of age at the start of the study. Forty behaviorally naive animals were studied in the resting state to document the effects of salt and/or nicotine on baseline arterial BP; the remaining 39 animals were used to study the effects of dietary salt and nicotine on the arterial BP conditional response. The rats were given food and water ad libitum. They weighed 250 and 300 g at the time of data acquisition. The animals were maintained on a low-salt (0.08% NaCl) or high-salt diet (8% NaCl) for 2 wk before nicotine or vehicle exposure (see Surgery). Both components of the study used four groups of rats: low salt + vehicle; low salt + nicotine; high salt + vehicle; and high salt + nicotine. The experiments were approved by the University of Kentucky Animal Care and Use Committee.

Behavioral conditioning. All rats were habituated to restraint in a soft conical sock for 1–2 d daily for 2 consecutive days. The 39 classically conditioned animals were trained in the behavioral paradigm commencing 1 wk after insertion of a minipump (see Surgery) to deliver either nicotine or vehicle. Once habituated to the sock restraint, these animals were presented with a series of pulsed and nonpulsed tones (defined as the CS+ and CS−, respectively). On each of 3 days, 5 of each 15-s tone were generated on a laboratory computer coupled to an external speaker; the tones were presented in pseudorandom pairs (e.g., CS+, CS−, CS+, CS−, CS+, etc.) at approximately 5-min intervals. On day 1, none of the first four sets of tones was followed by shock. The fifth and final CS+ tone on this first day was followed immediately by a 0.5-s tail shock. The shock intensity never exceeded 0.5 mA and was the minimum required to make the rat flinch and/or vocalize. Training continued for 2 more days; all CS+ tones were terminated with a tail shock. The CS− tone was never followed by shock. The animals were returned to their quarters after each daily session. Details of this conditioning paradigm have been published (23, 24).

Surgery. Two weeks after starting their respective diets, the animals were anesthetized with pentobarbital sodium (65 mg/kg ip) in preparation for surgical implantation of the minipump for drug administration. An Alza osmotic minipump filled with either nicotine (2.4 mg/kg · day−1; see Ref. 28) or vehicle (saline buffer) was inserted under the skin of the dorsal chest. Infusion of nicotine in this manner yields blood levels of 82 ± 9 ng/ml (28), equivalent to smoking two packs of cigarettes per day (28). Two weeks later, the animals were reanesthetized, as above, and a Teflon catheter (0.012 inch interior diameter) was implanted in the abdominal aorta by way of the femoral artery. The distal end of the catheter was tunneled under the skin, exited at the shoulders, and run through a flexible wire tether stabilized at the nape of the neck. The distal end was also glued to a piece of polyethylene-50 plastic tubing to facilitate coupling to a pressure transducer during data acquisition. After surgery, each animal was individually housed in a cage, supplied with food and water, with its movement only modestly restricted by the flexible tether.

Experimental procedures and protocol. Resting BP data were collected via the arterial catheter from the 40 nonconditioned subjects (10/group) 1 and 2 days after surgery (i.e., after ca. 4 wk on the high- or low-salt diet); arterial pressure was recorded for 11.2 min while the rat rested undisturbed in the sock. Behaviorally conditioned subjects were given 48 h to recover from surgery before data were collected. Each rat was introduced into the sock as usual, and five of each tone were presented. The animals were returned to their cages upon completion of the data session. The experimental sessions were conducted for 2 days. The numbers in each group were n = 7, low salt + vehicle; n = 10, low salt + nicotine; n = 11, high salt + vehicle; and n = 11, high salt + nicotine.

Data acquisition and analysis. BP was recorded in all cases by connecting the arterial catheter to a pressure transducer (Cobe model CDX-III). The pressure signal was recorded on a Grass model 7 polygraph. The BP data were digitally sampled at 10,000 Hz by using an analog-to-digital converter and an 80486 microprocessor. The pressure was averaged beat by beat over the 11.2 min in the behaviorally naive rats to yield a resting arterial pressure for each group of rats. In the conditioning study, data sampling began 9 s before a tone was presented and continued 6 s after the tone was stopped so that each 30-s recording covered the pretone baseline, tone, and recovery periods. The individual data files for all CS+ trials (and for all CS− trials) from a single subject were ensemble averaged to yield a single file depicting the conditional cardiovascular response for that animal; we have called this process a “high resolution analysis” (23). We defined pretone arterial BP to be the average mean pressure between 0 and 8 s. The first component of the conditional response (C1; see also Ref. 24) was taken as the peak value of mean BP between 10 and 12 s (that is, within the first 3 s of the tone’s sounding). The second component (C2) was taken as the average between 14 and 23 s. The unconditional response (UR) was the peak value between 24.5 s and 27 s, where the shock was presented at t = 24 s (where t is time). Data were tested by ANOVA, followed by post hoc Bonferroni t-tests when appropriate. Statistical significance was accepted for P < 0.05. All results are shown as means ± SD.

RESULTS

Extended (i.e., 11 min) arterial BP recordings were made in rats that had never been exposed to shock while they rested quietly in the shock restraint to determine a baseline across the various treatment groups (n = 10/group). Figure 1 summarizes these data. An ANOVA detected a significant group effect (F3,36 = 18.22). Resting mean arterial BP was higher in the high salt + nicotine group compared with each of the remaining groups. Likewise, placing the salt-sensitive rats on a high-salt diet alone (compare low/vehicle and high/vehicle in Fig. 1) increased BP. Conversely, the tests failed to detect any significant effect of nicotine treatment alone (compare low/vehicle and low/nicotine). Arterial BP was also determined during the 8-s preceding presentation of each tone for each behaviorally conditioned rat. The absolute values of these pretone BP values differed from the resting values, but, as above, the BP in the low salt + nicotine animals (138 ± 7 mmHg) did not differ from the low salt + vehicle rats (138 ± 8 mmHg). Likewise, for those animals on the high-salt diet, nicotine exposure tended (P = 0.056) to increase pretone BP (132 ± 7 mmHg).
compared with the vehicle-treated animals (124 ± 10 mmHg).

Figure 2 shows the 30-s CS+ trial recordings of arterial systolic, diastolic, and mean pressures for the high-salt + vehicle-treated group (n = 11). It was constructed by ensemble averaging the high resolution files over the 11 animals. The first (C1) and second (C2) components of the conditional response are indicated on the mean arterial pressure tracing. C1 consisted of a robust, but short-lived, pressor response. C2, on the other hand, was smaller but the increase in pressure was sustained above control until presentation of the tail shock. The UR is also indicated in Fig. 2; the first, and largest deflection, was closely associated with the rat’s physical flinching when the shock was delivered, whereas the smaller, second increase was the “physiological” component of the UR (24). In these animals, as in the Sprague-Dawley rat (24), there were only modest changes in heart rate during the CS+.

Figure 3 shows the same data for the high-salt + nicotine-treated animals (n = 11). The sensitivity of the arterial BP scales is the same as in Fig. 2, but the scale has been shifted upward in Fig. 3 to accommodate the increase in baseline pressure. The high salt + nicotine group also showed a robust C1 in response to CS+ but note the virtual absence of any C2 response.

Figure 4 summarizes these data in terms of absolute changes (Δ) in mean arterial BP measured against the respective pretone value for both CS+ (solid) and for CS− (hatched) trials. The conditional BP response for the low salt + vehicle group (n = 7) was characteristic of that typically evoked by the behavioral paradigm as evidenced by 1) a robust C1 (11 ± 2 mmHg) and smaller C2 (3 ± 2 mmHg), both of which significantly (horizontal line atop SD bar) exceed pretone control paired t-test with six degrees of freedom (t6) for C1 = 12.6; C2 = 4.5; and 2) discrimination between tones as evidenced by a C1 and C2 for CS+ that significantly
DISCUSSION

The discriminative classic conditioning paradigm is a particularly useful tool for studies such as those described here, because it permits a quantitative assessment of the subject’s learned response. In addition, a significant increase in arterial pressure with the same timing and general characteristics of C1 can be demonstrated in the Sprague-Dawley rat the first time the animal hears the tones—even before the tone is paired with the shock (25). It is reasonable to conclude, therefore, that C1 is not an acquired response, at least initially, but is, instead, a component of a startle or orienting response. If so, it is an innate response that requires no associative learning. Learned changes in the amplitude of C1 do eventually occur, however, because with progressive experience in the paradigm, the amplitude of C1 ultimately discriminates between CS+ and CS− in Sprague-Dawley (23, 24), spontaneously hypertensive, and WKY (15), and borderline hypertensive rats (3) that have not been exposed to nicotine. In stark contrast, there is no arterial BP change comparable to C2 when an animal first hears the tones (25); C2 is acquired only with training in the associative learning paradigm; it must be learned.

Our current findings should be interpreted with the foregoing background in mind. Qualitatively and quantitatively the conditional arterial BP response from the low salt + vehicle Dahl S rat is similar to what we have reported (23) in Sprague-Dawley rats on standard lab diet so that we may regard the Dahl-S animal’s conditional response when on the low-salt diet with vehicle as the control state. It is clear that simply increasing dietary salt had only a modest effect on the animal’s ability to learn and discriminate because 1) the amplitudes of C1 and C2 were only modestly depressed or unchanged (respectively) compared with control, and 2) both components evidenced discrimination between tones. Compared with this same control state, nicotine exposure alone did not demonstrably enhance or diminish the rat’s ability to acquire (i.e., learn) a generalized BP response to the tones because both C1 and C2 were significantly greater than pretone baseline; conversely, under the conditions of this experiment, nicotine alone impaired the rat’s ability to discriminate between CS+ and CS−.

The most telling findings are in the high salt + nicotine group. This group’s failure to show any significant differences between CS+ and CS− (i.e., both in C1 and C2) shows they did not discriminate between the two behavioral tests. In addition, these animals even failed to learn to associate the tone, whether steady or pulsed, with shock. Three observations support this last conclusion. First, they did not evidence a C2 response to CS+; recall that C2 is particularly characteristic of the learned response. Second, the amplitude of C1 was the same for both CS+ and CS−.

Note particularly that the virtual absence of C2 in high-salt exposure alone (i.e., low salt + nicotine) was indistinguishable from that evoked by CS− versus CS+. Note particularly the virtual absence of C2 in high-salt + nicotine group where nicotine alone impaired the rat’s ability to discriminate between the two behavioral tests. In addition, these animals even failed to learn to associate the tone, whether steady or pulsed, with shock. Three observations support this last conclusion. First, they did not evidence a C2 response to CS+; recall that C2 is particularly characteristic of the learned response. Second, the amplitude of C1 was the same for both CS+ and CS−.

![Graph](http://ajpheart.physiology.org/)

Fig. 4. Comparison of average change (Δ) ± SD in mean arterial BP with respect to baseline for the first (C1), and second (C2) components of the conditional response for CS+ (solid bars) and CS− (hatched bars) for each group of rats tested. UR shows peak BP change relative to that evoked by CS−. Note particularly the virtual absence of C2 in high-salt + nicotine group in the CS+ trials.

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Finally, the amplitude of C1 in the high salt + nicotine group was the same as for CS− in the control group. At least one question arises at this point, however. If the high salt + nicotine subjects failed to learn the tone-shock association, how do we account for the statistically significant ~6 mmHg C1 increase in arterial BP reported in the right column, first row of Fig. 4? We believe (see Perspectives) that this is an orienting or startle response that did not depend upon those central processes involved in associative learning and was not influenced by the experimental treatments.

We saw no between-group differences in the change in BP evoked by the shock. Whereas we are not aware of any studies concomitantly testing the effects of salt and nicotine exposure on unlearned responses, DiBona and Jones (8) have reported the effects of air-jet stress upon renal SNA and BP in several strains of rats, including borderline hypertensive rats fed either 1% or 8% NaCl. They reported that this form of stress increased renal SNA and BP in the rats maintained on 8% salt but not in those maintained on 1% salt. These data support an effect of salt exposure on an “innate” response. Moreover, the magnitude of the UR can vary, perhaps, at least in part, as a function of an animal’s acquiring the learned BP response (22). Therefore, whereas the similarity across all four groups of the pressor response to the shock (and to the cessation of the CS− tone) suggests that those pathways involved in expressing the UR, including the interface between the sympathetic nerve terminals and the effectors, are insensitive to nicotine exposure, this matter must remain an open question pending further study.

Arterial BP in the high-salt + vehicle and in the high-salt + nicotine-treated animals was elevated, raising the possibility that the different response patterns might be attributable to the higher baseline pressure. Our conclusions, however, were qualitatively similar when arterial BP response magnitude was evaluated as a percentage of baseline. Moreover, no “ceiling effect” was discernible in the amplitudes of the UR. We believe, therefore, that these differences in baseline arterial pressures do not explain the differences in the conditional response patterns.

The effects of nicotine on both physiology (e.g., BP regulation) and behavior (e.g., learning) are debated undoubtedly in part because the observed effects depend on a number of factors such as age (e.g., 2), gender (e.g., 29) and the nature of the behavioral task (e.g., 21). With respect particularly to the present findings, Perkins et al. (18) compared the changes in heart rate and BP in young, male smokers during combinations of a stress task and aerosol nicotine. They found that the pressor and tachycardia responses to a combination of nicotine and stress exceeded those to stress alone or to nicotine alone. Moreover, the same team also found that 1) the physiological and behavioral consequences of nicotine exposure depended on the subject’s baseline subjective state (19) and 2) may be transient, situationally specific, and partly gender dependent (20). We note particularly, therefore, that our findings apply specifically to physiologically mature, salt-sensitive rats trained in a discriminative behavioral conditioning paradigm and should not be extrapolated unadvisedly to other physiological conditions or behavioral paradigms.

Exposure to nicotine or nicotinic cholinergic receptor agonists has been reported to improve performance in some tasks (reviewed in Ref. 13), and, more specifically, to improve performance on a variety of memory tasks (reviewed in Ref. 14). Gould and Wehner (11) recently compared the effects of nicotine exposure in mice on a contextual learning versus associative learning (i.e., pairing of a conditional stimulus with an unconditional stimulus); they noted that “currently, no consensus exists on nicotine’s effects on either acquisition or retention of new information” (Ref. 11, p. 31). They report that 0.5 mg/kg nicotine, given on both training and testing days, improved contextual learning but had no effect on formation of a conditional response (freezing) to a tone that presaged a shock. Our data appear to support the latter conclusion but add the intriguing finding that nicotine exposure alone impairs the ability to discriminate between reinforced and nonreinforced tones. One interesting possibility [adapted from Levin and Simon (14, p. 219)] is that the magnitude of the C1 response was not smaller for CS− compared with CS+ in the low salt + nicotine group (i.e., failure to discriminate) because memory was facilitated to such an extent in these animals that they were unable to “forget” the pressor response evoked to both tones during the earliest training trials (25).

The present study examines the interactive effects of dietary salt and nicotine exposure on resting BP and on the BP response to acute behavioral stress in the Dahl-S rat, a strain of rat prone to hypertension on intake of elevated levels of dietary salt (4). We first examined the effects of the various treatments on rats that had never been exposed to the conditioning paradigm, including the shock; arterial BP was measured for ~11 min while these animals were resting quietly in the sock restraint (Fig. 1). Our findings with respect to nicotine exposure are similar to those reported by others. Whitescarver et al. (28) used a deoxycorticosterone acetate salt-sensitive rat preparation and found that chronic nicotine exposure significantly increased BP in the anesthetized animal compared with saline treatment. Chronic nicotine exposure also increases BP in the spontaneously hypertensive rat (7). Qualitatively, our findings are also in concert with recent tests using 24 h BP monitoring that detected higher BP in habitual smokers compared with nonsmokers during normal living conditions (19). However, the BPs in our nicotine and/or salt-treated, behaviorally conditioned animals during the pretone arterial pressures differed from those observed in our resting subjects. Likewise, Perkins et al. (19) concluded that the effects of nicotine on BP depend on the subject’s baseline subjective state. Bühler (6, p. 1793) has advanced the interesting hypothesis that “cigarette smoking acts as a pulsatile, exogenous amplifier of the sympathetic nervous sys-
of dietary salt and/or nicotine exposure may also de-

Perspectives. In other work, we have shown that C 1 is intim-
ately associated with an immediately preceding sudden burst in SNA (23). We believe this temporal relationship be-
 tween an antecedent change in SNA intimately associated with a subsequent increase in arterial BP evidences an open-loop response resultant from a “central command” (23). The sudden burst is fol-
ed immediately by a decrease in SNA (i.e., the “quiet period”) that is consistent with activation of the baroreflex by the C 1 pressor event (23). Finally, we have also speculated that C 2 results from an upward resetting of the baroreflex (23). If true, C 2 is influenced by a classical biofeedback loop. These physiological differences, together with the different patterns of ac-
quisition of the two components described in the intro-
duction and elsewhere (25) and the differential effect of nicotine on the startle versus learned components of the response, suggest that C 1 and C 2 are produced by dif-
f erent central neural processes. In this light, it is possible that nicotine acts preferentially on those pro-
cesses within the central nervous system involved in learning (possibly the amygdala?) compared with those involved in such processes as orientation to external stimuli (possibly the hippocampus or thalamic reticular nucleus?). Alternatively, because chronic nicotine and/or salt exposure depresses baroreflex function per se in both rats (e.g., 28) and humans (e.g., 10), it may be that nicotine thereby preferentially influences C 2. C 2 is not depressed in the spontaneously hypertensive rat (15) or in the borderline hypertensive rat on a high-salt diet (3). This alternative explanation, if correct, would imply that nicotine interferes primarily with the pro-
cesses responsible for expression of the learned re-
sponse rather than those mechanisms responsible for acquiring the learned response. Finally, whereas C 1 is produced by an increase in total peripheral resistance with no change in cardiac output, C 2 is produced by an increase in cardiac output (16). The differential effects of dietary salt and/or nicotine exposure may also de-
pend on these differences in the physiology of the conditional response.

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