The effects of deoxycorticosterone–induced sodium appetite on hedonic behaviors in the rat

Article in Behavioral Neuroscience - July 2006
Impact Factor: 2.73 - DOI: 10.1037/0735-7044.120.3.571 - Source: PubMed

4 authors, including:

Michael J Morris
University of Texas Southwestern Medical Center at Dallas
71 PUBLICATIONS 760 CITATIONS

Elisa S Na
University of Texas Southwestern Medical Center at Dallas
20 PUBLICATIONS 921 CITATIONS

Alan Kim Johnson
University of Iowa
335 PUBLICATIONS 9,846 CITATIONS
The Effects of Deoxycorticosterone-Induced Sodium Appetite on Hedonic Behaviors in the Rat

Michael J. Morris, Elisa S. Na, Angela J. Grippo, and Alan Kim Johnson
University of Iowa

The authors tested the hypothesis that chronic treatment with a dose of deoxycorticosterone acetate (DOCA) known to elicit a robust sodium appetite can negatively affect the hedonic state of rats. Daily treatment with DOCA with no opportunity to ingest saline produced a rightward shift in the midpoint (effective current 50) of lateral hypothalamic self-stimulation (LHSS) current-response functions and reduced intakes of a palatable sucrose solution. Providing rats with 0.3 M saline during DOCA treatment prevented the rightward shift in LHSS response functions and the decrease in sucrose intake. The authors concluded that a chronic sodium appetite, with no opportunity to attenuate the appetite, can elicit a reduced responsiveness to reward.

Keywords: mineralocorticoids, reward, salt appetite, intracranial self-stimulation, sucrose intake

Long-term alterations in body sodium balance can have negative physiological consequences. There is a well-established association between high dietary sodium intake and hypertension, renal disease, osteoporosis, and an accelerated risk of mortality in congestive heart failure (Devine, Criddle, Dick, Kerr, & Prince, 1995; MacGregor & de Wardener, 1998; Woolfson & de Wardener, 1996). Conversely, sodium deficiency can also have deleterious effects, and an adequate intake of sodium is required for maximal growth of bone and muscle during development as well as for integrity of the nervous system (Bursey & Watson, 1983; Fine, Ty, Lestrange, & Levine, 1987). Sodium is crucial to establishing the membrane potential of excitable cells, providing the “osmotic skeleton” of the extracellular fluids and in ensuring the appropriate hydromineral milieu for metabolic reactions throughout the body (Michell, 1995). Conditions such as profuse sweating, diarrhea, vomiting, hemorrhage, renal disease, and voluntary or treatment-imposed reductions in dietary intake will reduce body sodium. Multiple autonomic, endocrine, and behavioral mechanisms defend against severe depletion and generate behaviors to restore homeostasis (Johnson & Thunhorst, 1997; Michell, 1995).

A question that has rarely been addressed experimentally is whether body sodium homeostasis alters affective states. In humans, negative sodium balance produces many symptoms that resemble those of psychological depression, including fatigue, reduced appetite, impaired concentration, and altered sleep (McEwen, 1935). In the 1930s, McCance (1936) and his coworkers reported anorexia, exhaustion, and feeling “disinclined for physical or mental effort” (p. 825) as a result of self-imposed sodium deficiency (accomplished by combining a sodium-free diet with profuse sweating). Feeling exhausted is the primary symptom of chronic fatigue syndrome, a disease with a poorly understood etiology. A more recent study by Bou-Holaigah, Rowe, Kan, and Calkins (1995) reported that a subset of chronic fatigue subjects had voluntarily reduced their sodium intake. Therapy recommended an increase in sodium intake, along with fludrocortisone (a drug with sodium-retaining properties). Subsequently, 16 of 21 subjects reported a favorable response to therapy and, most interesting, an improved general sense of well-being (i.e., improved mood). It can be speculated that an increase in sodium ingestion or restoration of sodium balance may have contributed to the improvements in physiological and affective states.

Sodium deficiency activates the renin–angiotensin–aldosterone system, which promotes water ingestion and retention to defend against volume loss, and induces vasoconstriction to maintain blood pressure (Johnson & Thunhorst, 1997). Mineralocorticoid hormones (e.g., aldosterone) cause sodium retention at renal collecting ducts and also act on the brain to induce sodium appetitive and consummatory behaviors (Michell, 1995; Rice & Richter, 1943). Lucas, Pompei, and McEwen (1999) found that administration of the mineralocorticoid agonist deoxycorticosterone acetate (DOCA) for 11 days led to distinct neurochemical and neuuropeptidergic profiles in the ventral striatum that were dependent on availability of saline for ingestion. With no opportunity to attenuate the DOCA-induced sodium appetite, animals evidenced increased dopamine transporter ligand binding and increased enkephalin mRNA in the shell of the nucleus accumbens, suggesting decreased accumbal dopamine. The authors hypothesized that animals treated with DOCA without access to saline may be “anhedonic” (i.e., display decreased responsiveness to previously rewarding stimuli, a core symptom of major depressive disorder in humans; American Psychiatric Association, 2000) due to low levels of synaptic dopamine in the nucleus accumbens.
Conover, Woodside, and Shizgal (1994) found that acute treatment (1–2 days) with the diuretic–natriuretic furosemide did not alter subsequent lateral hypothalamic self-stimulation (LHSS) responding; however, 0.15 M saline more effectively competed with LHSS reward in forced-choice testing in rats that were sodium depleted compared with controls. The present studies were undertaken to determine whether chronic DOCA treatment and/or the attendant sodium appetite can decrease responding for rewarding stimuli in the rat. Two common behavioral measures of hedonic state were used: electrical self-stimulation of the brain (Edmonds & Gallistel, 1974; Grippo, Francis, Weiss, Felder, & Johnson, 2003) and intakes of a palatable sucrose solution (Griffiths, Shanks, & Anisman, 1992; Grippo, Beltz, & Johnson, 2003; Muscat & Willner, 1992). We used rightward shifts in LHSS current-response curves or reductions in sucrose intake to operationally define a hedonic deficit—that is, a decrease in the rewarding properties of the stimulus (Edmonds & Gallistel, 1974; Miliaressis, Rompre, Laviolette, Philippe, & Coulombe, 1986). We hypothesized that DOCA treatment may have dissociable effects on LHSS responding and sucrose intake depending on the rat’s ability to attenuate DOCA-induced sodium appetite via saline ingestion.

General Method

Animals

Male Sprague–Dawley rats (Harlan, Indianapolis, IN) weighing between 250 g and 350 g were used for all experiments and were maintained on a 12-hr light–dark cycle with ad libitum access to Teklad chow (Harlan Teklad, Madison, WI) and tap water, except where noted. Rats were housed individually in hanging wire-mesh cages and were adapted to the laboratory environment for at least 1 week prior to any experimental manipulation. Prior to experimentation, baseline daily water and 0.3 M (1.8%) saline intakes were determined for 3 days. All procedures were conducted in accordance with the National Institutes of Health (1986) Guide for the Care and Use of Laboratory Animals and were approved by the University of Iowa Animal Care and Use Committee.

Electrode Placement

Rats had bipolar stimulating electrodes (10-mm length; Plastics One, Roanoke, VA) chronically implanted in the lateral hypothalamus. The lateral hypothalamus was chosen for electrode placement on the basis of its relatively high reliability in producing self-stimulation behavior in rats (Olds, 1962). Under Equithesin anesthesia (3 ml/kg ip; University of Iowa Hospital Pharmacy, Iowa City), rats were placed in a stereotaxic instrument, and the head was leveled between bregma and lambda. The coordinates used were 3.0 mm posterior to bregma, 1.7 mm lateral to the midline, and 8.5 mm ventral to the skull surface. Four jeweler’s screws and dental acrylic were used to fix the electrode to the skull. Stadol (1 ml/kg sc; University of Iowa Hospital Pharmacy) was administered to the animals for postoperative analgesia. Rats were allowed to recover from surgery for at least 1 week prior to experimentation.

Self-Stimulation Training

Following a recovery period, rats were trained in a Plexiglas operant chamber equipped with a lever that delivered a 300-ms train of rectangular pulses of 1-ms duration (similar to previously reported stimulation parameters; Grippo, Francis, et al., 2003). Training consisted of 2 days of adaptation to the chamber and learning the association between lever pressing and current-pulse delivery. The electrical parameters were set to predetermined values (frequency = 60 Hz; current intensity = 250 μA) and were systematically varied with free pulses given until the rat began to respond by pressing the lever. Once the specific parameters were determined for each rat, these were held constant for the duration of the study (with the exception of current intensity, which was varied as described below). Rats that did not respond to electrical stimulation, displayed untoward motor effects, or did not achieve at least 30 responses per minute (RPMs) at 250 μA by the 2nd day of training were eliminated from the study (i.e., this was a functional assessment of successful electrode placement).

LHSS Current-Response Functions

Following LHSS training, baseline LHSS current-response functions were determined for each rat similar to methods described by Miliaressis et al. (1986) and Grippo, Francis, et al. (2003). Current was delivered in a descending series from 250 μA to 25 μA in 10 discrete presentations of 25-μA decrements. The rat was allowed to respond for 1 min at each current intensity. On each of 3 consecutive days, one current-response curve (see Figure 1 for a representative curve) was generated for each rat (RPMs at each of the 10 current intensities), and these were averaged to yield a single baseline curve. An optimal current-response curve was generated for each rat by using the following criteria: (a) the range of current intensities to which the rat responded was between 25 μA and 250 μA; (b) the response rate was minimal for low levels of current intensity (e.g., 25–75 μA) and increased monotonically, eventually reaching a plateau produced by presenting 10 consecutive increments of 25-μA current intensities, so that there was a sigmoid relationship between current intensity and behavioral responses ($r^2 > .80$); and (c) the maximum amount of current intensity for which the rat would respond also did not produce a motor effect. Data points were plotted using Sigma Plot (Jandel Scientific, Chicago) and were fitted to a three-parameter sigmoidal function from which three parameters were calculated: (a) maximum rate of responding, (b) current intensity that supports 50% of the maximum response rate effective current 50 (ECu50), and (c) minimum rate of responding.

Statistical Procedures

Mean ECu50 values were compared by using mixed-model analyses of variance (ANOVAs) and Bonferroni-corrected t tests. LHSS current-response functions following experimental manipulations were calculated identically to baselines. Decreased responsiveness to reward was evidenced by a significant increase in the midpoint of the curve (ECu50), representing

![Figure 1](image-url) A representative current-response function. Filled circles illustrate raw data points, and the solid line indicates the fit curve.
a rightward shift in the manipulation-induced current-response curve relative to the baseline current-response curve or by a significant decrease in sucrose intake relative to baseline. Body weights before and after experimentation were analyzed with Student’s t tests. Mixed-model ANOVAs and Bonferroni-corrected t tests were used for within- and between-group comparisons of baseline water, saline, and sucrose intakes with DOCA-induced water, saline, and sucrose intakes and to test the Group × Day of Injection interaction. A p value of less than .05 was required for statistical significance.

Experiment 1a: Effects of DOCA Treatment on LHSS

Method

Following recovery from electrode implantation surgery, baseline LHSS current-response functions were calculated and established for each rat as described above. On the day following LHSS baseline testing, rats were given a subcutaneous DOCA (10 mg/kg; n = 12) or sesame oil vehicle (VEH; n = 7) injection each day for 11 days. The first day of DOCA or VEH injection was considered Day 1 of the experiment. LHSS testing (POST) was conducted on Day 4 through Day 6. Following testing and generation of LHSS-POST current-response functions, rats were given access to 0.3 M saline. Intakes were recorded on Day 7 through Day 12 to determine whether DOCA treatment had induced a significant sodium appetite. Because of the experimental protocol, it was not possible to determine at which day saline intakes were significantly elevated as rats were denied saline access on Days 1–6 of the experiment.

Results

There was a sigmoidal relationship between current intensity and response rate for LHSS. As current intensity increased, response rates also increased, approaching an asymptote. Rats given daily injections of DOCA displayed a rightward shift of their current-response functions, whereas VEH-treated rats had virtually identical baseline versus POST current-response curves (see Figure 2). There was a significant interaction effect for Group × Baseline versus POST ECu50 values, F(1, 17) = 9.39, p < .01; main effects were nonsignificant. Post hoc tests showed that DOCA-injected rats had a significantly increased ECu50 relative to their baselines, t(11) = 3.45, p < .027, whereas VEH-injected rats did not significantly differ in their baseline versus POST values (see Figure 3). The maximum number of lever presses per minute did not differ between groups or between the baseline and POST values within the DOCA- and VEH-treated groups (see Table 1 for mean minimum and maximum responses and ECu50 values). An equivalent number of lever presses at the maximum current intensity provides evidence that the capacity to lever press was not nonspecifically compromised by DOCA treatment.

Figure 4 shows daily saline intakes of the DOCA- and VEH-injected groups beginning on Day 7 of injection and continuing until the day after the final injection (Day 12). A DOCA-induced sodium appetite was evident by the 1st day that intakes were recorded, t(17) = 9.35, p < .001, and remained elevated relative to the VEH-treated group for the duration of testing (p < .05). Baseline saline intakes, as well as body weights before and after testing, did not significantly differ between DOCA- and VEH-treated rats (mean saline: DOCA = 4.88 ml ± 1.31 ml; VEH = 4.69 ml ± 1.35 ml; mean body weight before: DOCA = 367.67 g ± 5.75 g; VEH = 361 g ± 7.65 g; mean body weight after: DOCA = 401.58 g ± 6.54 g; VEH = 406.5 g ± 9.78 g).

Experiment 1b: Time Course of DOCA-Induced Sodium Appetite

Method

As stated previously, the design of Experiment 1a precluded giving access to saline solutions to test for the presence of sodium appetite over the same period the rats were being tested for LHSS responding. Consequently, a comparable group of rats was given daily subcutaneous injections of DOCA (10 mg/kg in 1 ml/kg sesame oil; n = 7) or an equivalent-volume VEH injection (n = 6) at approximately 1300 each day for 11 days. Daily intakes of 0.3 M NaCl and water were recorded in 100-ml graduated cylinders suspended from the animals’ home cages.
Results

As has been shown previously (Rice & Richter, 1943), daily DOCA treatment elicited robust intakes of both 0.3 M NaCl and water. In the current study, saline intakes were significantly increased by Day 3 of injection—that is, the 2nd day of recording intakes—\( t(10) = 2.73, p = .033 \), and remained elevated for the duration of the experiment: Group \( \times \) Day of Injection, \( F(16, 160) = 3.59, p = .001 \); main effect for group, \( F(1, 10) = 9.14, p = .013 \); main effect for day of injection, \( F(16, 160) = 3.44, p = .001 \) (see Figure 5). Water intakes paralleled the saline intakes (data not shown). It has been shown that elevated water intake in DOCA-treated rats that are provided with both water and saline to drink is secondary to saline intake and likely represents an effort by the rat to maintain osmotic balance (Rice & Richter, 1943). At no time point was there any evidence of increased saline intake (see Figure 5) or water intake (not shown) in the VEH-treated group. Baseline saline intakes and body weight before and after experimentation were not significantly different between groups (mean saline: DOCA = 3.96 ml ± 1.53 ml; VEH = 4.22 ml ± 1.42 ml; mean body weight before: DOCA = 341.71 g ± 9.50 g; VEH = 356.17 g ± 11.17 g; mean body weight after: DOCA = 374.86 g ± 11.44 g; VEH = 389.17 g ± 10.11 g).

Experiment 2: Effects of DOCA Treatment With or Without Saline Access on LHSS Responding

Method

A repeated measures, counterbalanced, crossover design was used to address whether saline availability and consumption could ameliorate the

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Maximum RPMs</th>
<th>Midpoint ( (\text{EC}_{50}; \text{standardized current level}) )</th>
<th>Minimum RPMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCA (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80.50 ± 3.64</td>
<td>4.94 ± 0.28</td>
<td>1.92 ± 0.45</td>
</tr>
<tr>
<td>POST</td>
<td>74.37 ± 5.44</td>
<td>6.67 ± 0.34</td>
<td>1.34 ± 0.64</td>
</tr>
<tr>
<td>Vehicle (n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>73.96 ± 3.86</td>
<td>5.44 ± 0.32</td>
<td>2.38 ± 1.23</td>
</tr>
<tr>
<td>POST</td>
<td>80.98 ± 8.13</td>
<td>5.08 ± 0.26</td>
<td>2.25 ± 0.77</td>
</tr>
</tbody>
</table>

Note. DOCA = deoxycorticosterone acetate; RPM = response per minute; \( \text{EC}_{50} \) = effective current 50; POST = lateral hypothalamic self-stimulation testing following treatment. *\( p < .05 \) vs. respective baseline value.
DOCA-induced rightward shift in LHSS current-response functions observed in Experiment 1a. The protocol for this experiment was identical to Experiment 2 except that all rats (N = 18) in Experiment 2 were given daily DOCA injections (10 mg/kg) for the duration of the experiment. Following generation of LHSS baselines, treatment order was counterbalanced in the following fashion. Rats in the with saline (WS) → no saline (NS) group (n = 10) were provided saline on Days 1–6 and denied saline on Days 7–12. LHSS testing was conducted on Days 4–6 (WS phase) and Days 10–12 (NS phase). Saline intakes were recorded during the period of saline availability. Animals in the NS → WS group (n = 8) were denied saline on Days 1–6 and provided saline access on Days 7–12. Thus, the following comparisons were possible with respect to the EC_{50} values: baseline versus WS, baseline versus NS, and WS versus NS.

**Results**

An analysis of the LHSS EC_{50} data (see Figure 6) with treatment orders combined revealed a significant global F ratio, F(1, 17) = 5.83, p = .27. As shown in Experiment 1a, DOCA-treated rats that were denied access to saline showed a significant increase in EC_{50} relative to baseline, t(17) = 6.68, p < .001 (Figure 6). This increase was attenuated when saline was made available during DOCA treatment (the WS vs. baseline comparison was not statistically significant). Also, EC_{50} values during the NS phase were significantly higher than EC_{50} values observed during the WS phase, t(17) = 5.47, p < .001. With respect to statistical significance, the results were identical when the individual treatment orders were analyzed separately. It is evident from Figure 6 that DOCA treatment with NS available produces a rightward shift in LHSS current-response functions. Although saline availability during DOCA treatment yielded EC_{50} values that were not statistically different from baseline, it appears that the WS function slightly shifted to the right. The maximum number of RPMs did not differ between the conditions (see Table 2 for maximum and minimum number of RPMs and EC_{50} values).

**Experiment 3a: Effects of DOCA Treatment on 2% Sucrose Intake**

**Method**

Prior to DOCA treatment, rats were adapted to the taste of a 2% sucrose solution. Food and water bottles were removed, and rats were acclimated to a 1-hr period of sucrose availability in their home cages at the same time each day (1100–1200). Following at least 1 week of adaptation to the sucrose availability schedule, 1-hr baseline intakes were taken as the mean of five separate tests conducted on alternate days. On the day following the final baseline test, rats were randomly assigned to receive daily DOCA (10 mg/kg; n = 8) or VEH treatment (n = 8) for 11 days. A total of five sucrose tests was then given every other day beginning on the 3rd day of DOCA or VEH treatment. Statistical analyses were carried out by using the mean of the five baseline and treatment (“test”) values, respectively. To assess whether treatment produced a nonspecific decrease in drinking behavior, we calculated baseline 24-hr water intakes as an average of 3 days and subsequently compared these values with measurements made periodically throughout treatment (Days 4, 7, and 10 of treatment).

**Results**

A repeated measures ANOVA on baseline mean versus test mean intakes for DOCA- and VEH-treated rats revealed a significant interaction effect, F(1, 14) = 5.830, p = .001. Sucrose intakes during the test period were significantly lower than the baseline intakes in the DOCA-treated group, t(7) = 4.791, p = .002, whereas the test intakes of the VEH-treated group were not significantly different from their respective baselines (see Figure 7). There was no evidence of any between- or within-group difference in water intakes (see Figure 7).

**Experiment 3b: Effects of DOCA Treatment With or Without Saline Access on 2% Sucrose Intake**

**Method**

To determine whether saline availability during treatment could prevent the reduction in sucrose intakes observed in Experiment 3a, we randomly assigned rats to the following three groups: the WS group (n = 7), which was provided 0.3 M saline ad libitum during DOCA treatment; the NS group (n = 6), which was not provided saline during treatment; and the VEH group (n = 5), which was also not provided saline during treatment.
unequal group ns were a result of either attrition or failure to drink sucrose solution during the adaptation period, respectively. Adaptation to the sucrose availability schedule, baseline and test intakes, and statistical analyses were carried out identically to Experiment 3a. In addition, a recovery period was included and assessed as follows: After the completion of DOCA or VEH treatment, all rats were allowed access to 0.3 M saline for a period of 3 days. Rats were then given three additional sucrose intake tests, which were conducted on alternate days (i.e., the 3rd, 5th, and 7th days after treatment).

Results
With respect to sucrose intake, there was a significant interaction effect for baseline, test, and Recovery Intakes × Group, F(4, 30) = 6.149, p = .01. Test intakes were significantly lower than baseline, t(5) = 4.10, p = .009, and recovery intakes, t(5) = 3.233, p = .021, for the NS group (see Figure 8). However, for the WS group, test intakes did not significantly differ from baseline or recovery intakes, suggesting that saline availability prevented the hedonic deficit observed in Experiment 3a (test intakes also were not different from baseline or recovery intakes for the VEH group).

Similar to LHSS responding in Experiment 2, saline availability during DOCA treatment did not entirely prevent a trend toward hedonic deficit. It is apparent from Figure 8 that intakes during the test period in the WS group were reduced relative to baseline intakes, although this reduction did not reach statistical significance. By contrast, sucrose intakes increased in the control group in all three phases of the experiment.

Discussion
In the present study, daily DOCA treatment produced a decrease in responding for reward as evidenced by a rightward shift in the EC<sub>50</sub> of LHSS current-response curves and by a reduction in sucrose intake. Reduced responsiveness to reward was present when the animals were tested following 4–6 days of DOCA treatment, a time in which a significant sodium appetite would have already developed (Experiment 1b). The effect of DOCA treatment on LHSS responding and sucrose intake could be significantly ameliorated by providing 0.3 M saline for consumption during treatment. The present study, to our knowledge, is the first to use behavioral measures to demonstrate a reduction in responding for rewarding stimuli as a result of a chronic sodium appetite in rats.

The findings in the current study are in accord with the hypothesis of Lucas et al. (1999) that rats with a significant and persistent sodium appetite are anhedonic. Their claim was based on neurochemical changes in putative neural reward centers following DOCA treatment. Specifically, they found that DOCA-treated rats had increased dopamine transporter ligand binding and increased enkephalin mRNA in the nucleus accumbens (measured following 11 days of treatment) if the animals were denied saline, suggesting a decrease in synaptic dopamine. Dopamine levels in the ventral striatum (e.g., nucleus accumbens) are believed to be involved in mediating reward (Wise & Rompre, 1989) and are reduced in animals subjected to chronic stress paradigms and in various animal models of depression (Cabib & Puglisi-Allegra, 1996; Zacharko & Anisman, 1991). It has been proposed that low levels of dopamine in the mesolimbic dopamine pathway play a role in depression induced by chronic stress (Cabib & Puglisi-Allegra,

### Table 2

**Mean (± SEM) Curve Parameters Defining Current-Response Functions in DOCA-Treated Rats With vs. Without Access to 0.3 M Saline**

<table>
<thead>
<tr>
<th>Group</th>
<th>Maximum RPMs</th>
<th>Midpoint (EC&lt;sub&gt;50&lt;/sub&gt;; standardized current level)</th>
<th>Minimum RPMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>80.54 ± 3.12</td>
<td>5.43 ± 0.17</td>
<td>1.34 ± 0.20</td>
</tr>
<tr>
<td>With saline</td>
<td>74.64 ± 2.94</td>
<td>5.81 ± 0.15</td>
<td>1.53 ± 0.30</td>
</tr>
<tr>
<td>No saline</td>
<td>77.88 ± 3.99</td>
<td>7.22 ± 0.46†*</td>
<td>1.10 ± 0.21</td>
</tr>
</tbody>
</table>

Note. DOCA = deoxycorticosterone acetate; RPM = response per minute; EC<sub>50</sub> = effective current 50. † p < .05 vs. with saline value. *p < .05 vs. baseline value.
The mesolimbic dopamine system and particularly one of its forebrain terminal regions, the nucleus accumbens, may also be involved in sodium appetite behavior. Saline intake in sodium-depleted rats elicits dopamine release in the nucleus accumbens (Hoebel, Hernandez, Schwartz, Mark, & Hunter, 1989), and blockade of dopamine D2 receptors attenuates sham saline drinking in sodium-depleted rats (Roitman, Schafe, Thiele, & Bernstein, 1997). Structural changes in the nucleus accumbens are also observed as a result of sodium depletion. Repeated depletions in rats lead to increases in the number of dendritic spines in nucleus accumbens neurons (Roitman, Na, Anderson, Jones, & Bernstein, 2002). Increased expression of the immediate early gene c-fos is also observed in the nucleus accumbens in rats experimentally depleted of sodium (Na, Johnson, Beltz, Morris, & Johnson, 2004). Changes in accumbens neurochemistry would suggest one potential mechanism to explain the hedonic deficits observed in the current studies. Electrical stimulation of the medial forebrain bundle and lateral hypothalamus and sucrose ingestion have been shown to elicit increased dopamine release in the accumbens (Hoebel et al., 1989; You, Chen, & Wise, 2001). Changes in dopaminergic neurotransmission within the accumbens as a result of chronic DOCA treatment and/or a persistent sodium appetite could potentially diminish responding for stimuli that utilize the accumbens as a neural substrate for the processing of reward.

Rats with experimentally induced heart failure develop chronically elevated 0.3 M NaCl intakes (Francis, Weiss, Wei, Johnson, & Felder, 2001). It is interesting to note that in a study in which no saline solution was available for consumption, heart failure rats also displayed rightward shifts in LHSS current-response curves (Grippo, Francis, et al., 2003). There is a well-established comorbidity relationship between cardiovascular disease and depression in humans, and there are several hypotheses regarding the biological basis of this relationship (Grippo & Johnson, 2002; Joynt, Whellan, & O’Connor, 2003). The endocrine profiles of sodium deficiency and heart failure are similar. Increased angiotensin II and aldosterone levels as well as increased sympathetic outflow are observed in both cases (Johnson & Thunhorst, 1997; Katz, 2000).

It is possible that similar mechanisms engaged in sodium deficiency and heart failure may produce hedonic deficits in both circumstances, given that similar endocrine, sympathetic, and behavioral adjustments occur. The animals in the present study were not sodium depleted but instead had a pharmacologically induced sodium appetite. However, we have also recently found that diuretic-induced water and sodium loss produces a similar rightward parallel shift in LHSS responding in rats tested 48 hr after depletion by using stimulation parameters identical to those used in the current study. The shift in responding for LHSS was ameliorated if rats were allowed to restore sodium balance by giving them access to saline (Grippo, Moffitt, Beltz, & Johnson, 2006).

The effects of mineralocorticoid hormones on affective state have scarcely been studied, whereas glucocorticoid effects have received significant attention (De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Holsboer, 2000). An emerging hypothesis in the literature regarding the biology of affective disorders is that alterations in central mineralocorticoid receptor levels, particularly in the hippocampus, may play a role in stress-induced anhedonia and depression (De Kloet et al., 1998; Lopez, Chalmers, Little, & Watson, 1998). However, the bulk of the studies to date have focused on the effects of chronic corticosterone (the rat analogue of the human glucocorticoid cortisol) on central mineralocorticoid receptors as well as on affective state (De Kloet et al., 1998; Lopez et al., 1998). A recent study in humans who have major depression found increases in aldosterone levels in participants with depression versus participants without depression (Murck et al., 2003). Although their data are correlational in nature, these authors suggested that aldosterone levels may be a sensitive marker of depression. Similarly, a recent study from our laboratory found increased aldosterone levels, as well as plasma renin activity, in the chronic mild stress rodent model of depression (Grippo, Francis, Beltz, Felder, & Johnson, 2005).

The results of the current study suggest that it is the state of a chronic, attenuated sodium appetite that produces a hedonic deficit, rather than mineralocorticoid treatment per se. When rats were treated with DOCA and provided ad libitum saline access, we failed to find statistically significant changes in LHSS responding or sucrose intake. However, in both the LHSS and sucrose experiments, there remained a trend toward hedonic deficit (i.e., a slight rightward shift in EC50 and decrease in sucrose intake). A state of persistent sodium hunger, or “craving,” regardless of its method of induction, may be capable of altering reward sensitivity. In the current study, relief from sodium craving essentially prevented the hedonic disturbance observed in sodium-hungry animals. However, it cannot be ruled out that mineralocorticoid hormones are capable of producing significant hedonic disturbances when administered over a longer time course. It is also unknown whether forms of sodium appetite that are purely mineralocorticoid independent (e.g., adrenalectomy) can also decrease responding for rewarding stimuli. An alternative explanation for our results that cannot be entirely ruled out is that DOCA-treated animals experienced malaise that affected their motivation and/or ability to engage in rewarding behaviors. However, although latencies to drink sucrose were not recorded, DOCA-treated rats and controls approached and sampled from the drinking spouts almost immediately upon presentation. Also, body weights and maximum number of RPMs for LHSS were not different between groups. DOCA-
treated rats could not be distinguished from controls on the basis of casual observation of their alertness or level of motor activity.

In conclusion, we found that rats with a chronic, unattenuated sodium appetite evidenced decreased responsiveness to reward by using two common behavioral indices of reward efficacy, intracranial self-stimulation and sucrose ingestion. Both methods have been used extensively to assess hedonic disturbances in animals subjected to repeated-stress paradigms (Griffiths et al., 1992; Grippo, Beltz, & Johnson, 2003; Grippo, Francis, et al., 2003; Zacharko & Anisman, 1991). A chronic sodium appetite, or salt hunger, may be akin to a chronic stressor capable of producing similar behavioral outcomes as those observed in more commonly used stress paradigms. Chronic homeostatic dysregulation and disease have profound effects on hedonic state. Our results corroborate previous observations in humans that a prolonged sodium deficiency can negatively impact hedonic state. These findings may have important implications for diseases of cardiovascular and body fluid homeostasis (e.g., congestive heart failure, sodium deficiency) where sodium appetite is increased and for affective disorders.

References


Received November 2, 2005
Revision received February 20, 2006
Accepted March 6, 2006

Members of Underrepresented Groups: Reviewers for Journal Manuscripts Wanted

If you are interested in reviewing manuscripts for APA journals, the APA Publications and Communications Board would like to invite your participation. Manuscript reviewers are vital to the publications process. As a reviewer, you would gain valuable experience in publishing. The P&C Board is particularly interested in encouraging members of underrepresented groups to participate more in this process.

If you are interested in reviewing manuscripts, please write to the address below. Please note the following important points:

- To be selected as a reviewer, you must have published articles in peer-reviewed journals. The experience of publishing provides a reviewer with the basis for preparing a thorough, objective review.

- To be selected, it is critical to be a regular reader of the five to six empirical journals that are most central to the area or journal for which you would like to review. Current knowledge of recently published research provides a reviewer with the knowledge base to evaluate a new submission within the context of existing research.

- To select the appropriate reviewers for each manuscript, the editor needs detailed information. Please include with your letter your vita. In the letter, please identify which APA journal(s) you are interested in, and describe your area of expertise. Be as specific as possible. For example, “social psychology” is not sufficient—you would need to specify “social cognition” or “attitude change” as well.

- Reviewing a manuscript takes time (1–4 hours per manuscript reviewed). If you are selected to review a manuscript, be prepared to invest the necessary time to evaluate the manuscript thoroughly.

Write to Journals Office, American Psychological Association, 750 First Street, NE, Washington, DC 20002-4242.