Effects of aging on mineralocorticoid-induced salt appetite in rats

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Thunhorst RL, Beltz TG, Johnson AK. Effects of aging on mineralocorticoid-induced salt appetite in rats. Am J Physiol Regul Integr Comp Physiol 305: R1498–R1505, 2013. First published October 16, 2013; doi:10.1152/ajpregu.00349.2013.—This work examined the effects of age on salt appetite measured in the form of daily saline (i.e., 0.3 M NaCl) drinking in response to administration of deoxycorticosterone acetate (DOCA; 5 mg/kg body wt) using young (4 mo), “middle-aged” adult (12 mo), and old (30 mo) male Brown Norway rats. Water and sodium intakes, excretions, and balances were determined daily. The salt appetite response was age dependent with “middle-aged” rats ingesting the most saline solution followed in order by young and then old rats. While old rats drank the least saline solution, the amounts of saline ingested still were copious and comprise an unambiguous demonstration of salt appetite in old rats. Middle-aged rats had the highest saline preference ratios of the groups under baseline conditions and throughout testing consistent with an increased avidity for sodium taste. There were age differences in renal handling of water and sodium that were consistent with a renal contribution to the greater saline intakes by middle-aged rats. There was evidence of impaired renal function in old rats, but this did not account for the reduced saline intakes of the oldest rats.

METHODS

Animals. Male BN rats aged 4 mo (young, n = 6), 11 mo (“middle-aged” adult, n = 6), and 28–29 mo (old, n = 6) were obtained from Harlan (Indianapolis, IN) through services provided by the National Institute on Aging (NIA). They were housed individually in hanging stainless steel cages in a temperature-controlled room (23°C) on a 12:12 light-dark cycle with lights on at 7:00 AM. They received ad libitum access to standard Teklad Rodent Diet and tap water. Rats were allowed 3–4 wk for adaptation and were tested at ~5, 12, and 30 mo of age, respectively. All procedures were approved by the University of Iowa Institutional Animal Care and Use Committee.

Drugs. DOCA was obtained from Sigma-Aldrich (St. Louis, MO). It was dissolved in propylene glycol (Fisher Scientific, Fair Lawn, NJ) at 8 mg/ml and administered subcutaneously.

Procedures: water and sodium intakes, excretions, and balances during daily injections of DOCA. At least 7 days before testing was started, rats were provided access to 0.3 M NaCl and distilled water. At least 3 days before the testing, pelleted sodium-deficient diet (MP Biomedicals, Aurora, OH) was substituted for the standard diet. To begin testing, the rats were placed in standard stainless steel metabolism cages with stainless steel funnels beneath. Ground sodium-deficient diet was available from a stainless steel cup through an opening in the back of the cage. Graduated cylinders with attached drinking spouts were filled with distilled water and 0.3 M NaCl and attached to the front of the cages. Urine was collected into preweighed beakers placed beneath the funnels.

Baseline measures were obtained for 5 days followed by treatment measures for 6 days and recovery for 2 days. Treatment consisted of daily subcutaneous injections of DOCA at 5 mg/kg body wt. Daily measurements were obtained between 0800 and 0900 h. Each morning, the water and saline intakes were read, the urine beaker and food cup were collected, and the rat was weighed. Distilled water was used to rinse the floor of the cage and funnel to collect residual salt. This wash volume was collected into a separate preweighed beaker. Then a clean funnel was placed underneath the cage with a new beaker. The food cup was weighed, “topped off” with fresh ground diet, and reweighed before being placed back in the cage. Food spillage was collected and considered in the daily measures. The rat was returned to the cage, and water and saline cylinders were reattached. On test
days, the rat received an injection of DOCA before returning to the cage.

Urine and wash volumes were determined by weight (i.e., 1 g = 1 ml). Samples were refrigerated for later analysis. The urine and wash were analyzed for sodium and potassium content. Sodium and potassium excretions included the amounts of sodium and potassium lost in the urine plus the wash. Water balance was calculated as total fluid intake (i.e., water + saline) minus urine volume. Sodium balance was calculated as 0.3 M NaCl intake minus urinary sodium excretion.

Urine analysis. Urine was measured for volume (UV). Urinary sodium and potassium concentrations (UNa and UK) were determined by ion-specific electrodes (NOVA Biomedical, Waltham, MA) and were used for calculation of urinary sodium and potassium excretions (UNaV and UKV).

Statistical analysis. Data were analyzed by one-way analysis of variance (ANOVA) with age as the between-subjects factor or by two-way ANOVA with days as the within-subjects factor and age as the between-subjects factor. Planned comparisons were made with Fisher’s least significant difference tests when the global F ratio was significant. Values are significant at P < 0.05.

RESULTS

Body weights. Body weights (BWs) for the age groups were significantly different throughout testing (age main effect: F_{2,15} = 34.18; P < 0.001). Initial BWs at 5, 12, and 30 mo were 333 ± 7, 418 ± 14, and 448 ± 5 g, respectively. Beginning the first day of DOCA treatment, BW increased significantly compared with average baseline values for all age groups (days main effect, F_{10,150} = 11.53, P < 0.001). There were no other significant effects. Because of the significant differences in BW between the ages, most measures were analyzed both as absolute and as BW-adjusted values. The results for absolute and BW-adjusted measures generally paralleled one another with a few differences. While the results of both analyses are described in detail, only BW-adjusted results are presented with figures.

Daily intake measures. On an absolute basis, old rats drank significantly more water than young and middle-aged rats throughout the experiment (Age main effect, F_{2,15} = 8.93; P < 0.01). Water intakes for all groups were significantly reduced during DOCA treatment compared with baseline values (Days main effect, F_{10,150} = 17.27; P < 0.001). Saline intakes during baseline were not different between groups and increased significantly for all ages beginning on the first day of DOCA treatment (Age × Days interaction, F_{20,150} = 9.14; P < 0.001). Saline intakes were significantly higher for middle-aged rats compared with both other groups by the second day of DOCA treatment. Food intakes during baseline were highest for old rats (Age × Days interaction, F_{20,150} = 6.51; P < 0.001). DOCA treatment significantly reduced food intakes of middle-aged and old rats but not of young rats.

All effects for BW-adjusted water, saline, and food intakes (i.e., ml or g/100 g body wt) were significant (Fig. 1). On a BW basis, middle-aged rats drank significantly less water than baseline days and on the first day of DOCA treatment compared with both young and old rats (Age × Days interaction, F_{20,150} = 2.20; P < 0.01). During DOCA treatment, water intakes declined significantly for all groups, but especially for young rats, and were significantly higher for old rats compared with both other groups. There were no age differences in BW-adjusted saline intakes during baseline. However, there were significant age-related increases in saline intakes during DOCA treatment in the following order: middle-aged rats > young rats > old rats (Age × Days interaction, F_{20,150} = 8.33; P < 0.001). On a BW basis, old rats ate significantly more food than the other groups during baseline (Age × Days interaction, F_{20,150} = 5.59; P < 0.001). BW-adjusted food intakes decreased significantly during DOCA for both middle-aged and old rats but not for young rats.

Saline preference was calculated as the ratio of saline intake to total fluid intake. All effects for saline preference ratio were significant. During baseline, middle-aged rats had significantly higher saline preference ratios compared with those of both young and old rats, owing primarily to their reduced water intakes compared with the other groups (Age × Days interaction, F_{20,150} = 2.87; P < 0.001, Fig. 2). Saline preference ratios of young and old rats did not differ during baseline. All groups had significantly elevated saline preference ratios beginning the first day of DOCA treatment. During DOCA, saline preference ratios were initially highest for middle-aged rats but were matched by those of young rats by the fourth day of treatment. Old rats had significantly reduced saline preference ratios compared with both young and middle-aged rats throughout DOCA treatment.
Significantly different from both the other groups, both young and middle-aged rats. Water balances were significantly age related during baseline with old rats having the highest total fluid intakes and old rats having the lowest total fluid intakes (Age × Days interaction, $F_{20,150} = 7.69; P < 0.001$) (Fig. 3). Similarly, BW-adjusted urinary volumes did not differ between groups during baseline and increased significantly for all groups during treatment, with middle-aged rats having significantly higher urinary volumes compared with both young and old rats during treatment (Age × Days interaction, $F_{20,150} = 8.00; P < 0.001$). BW-adjusted water balances were significantly lower for old rats compared with young and middle-aged rats during baseline (Age main effect, $F_{2,15} = 14.24; P < 0.001$). BW-adjusted water balances were significantly higher on the first day of DOCA treatment for all groups compared with all other days, and there were no significant differences between any other days (Days main effect, $F_{10,150} = 4.13; P < 0.001$). Young rats had significantly higher water balances on the first day of DOCA treatment compared with the other groups, particularly when the balance measures were normalized according to average baseline values.

Daily water balance measures. Total (i.e., water + saline) fluid intakes and urine volumes were used to calculate water balances. On an absolute basis, total fluid intakes were equivalent between groups during baseline and increased significantly for all ages beginning the first day of DOCA treatment (Age × Days interaction: $F_{20,150} = 8.52; P < 0.001$). During treatment, total fluid intakes were significantly higher for middle-aged rats compared with those of both young and old rats and were not different between young and old rats. The increased fluid intakes on the first day of DOCA were accompanied by increases in BW for all ages (Days main effect: $F_{10,150} = 11.53; P < 0.001$, Table 1). Absolute urine volumes were significantly age related during baseline with old rats excreting the most and young rats excreting the least (Age × Days interaction, $F_{20,150} = 8.48; P < 0.001$). Absolute urine volumes increased significantly for all ages during DOCA treatment with middle-aged rats developing significantly greater urine volumes than both young and old rats. Absolute water balances depended on Age (main effect, $F_{2,15} = 5.77; P < 0.001$) and Days (main effect, $F_{10,150} = 4.10; P < 0.001$). Old rats had significantly lower water balances compared with both young and middle-aged rats. Water balances were significantly higher on the first day of DOCA compared with all other days.

BW-adjusted total fluid intakes were not different between groups during baseline. Total fluid intake increased significantly for all groups during DOCA treatment, with middle-aged rats having the highest total fluid intakes and old rats having the lowest total fluid intakes (Age × Days interaction, $F_{20,150} = 7.69; P < 0.001$) (Fig. 3). Similarly, BW-adjusted urinary volumes did not differ between groups during baseline and increased significantly for all groups during treatment, with middle-aged rats having significantly higher urinary volumes compared with both young and old rats during treatment (Age × Days interaction, $F_{20,150} = 8.00; P < 0.001$). BW-adjusted water balances were significantly lower for old rats compared with young and middle-aged rats during baseline (Age main effect, $F_{2,15} = 14.24; P < 0.001$). BW-adjusted water balances were significantly higher on the first day of DOCA treatment for all groups compared with all other days, and there were no significant differences between any other days (Days main effect, $F_{10,150} = 4.13; P < 0.001$). Young rats had significantly higher water balances on the first day of DOCA treatment compared with the other groups, particularly when the balance measures were normalized according to average baseline values.

Daily urinary electrolyte concentrations and excretions. Urinary sodium concentrations during baseline were significantly higher for middle-aged rats compared with the other groups (Fig. 4). Urinary sodium concentrations increased significantly for all ages in response to DOCA. However, urinary sodium concentration of young rats increased sufficiently to match that of middle-aged rats while urinary sodium concentration of old rats remained significantly reduced compared with both of the other groups (Age × Days interaction, $F_{20,150} = 3.28; P < 0.001$). Urinary potassium concentrations during baseline were significantly lower for old rats compared with the other groups (Age × Days interaction, $F_{20,150} = 2.35; P < 0.01$). Urinary potassium concentrations decreased significantly for all groups during DOCA treatment, particularly for middle-aged rats. The urinary potassium concentrations for middle-aged rats were significantly reduced from baseline values beginning the first day of DOCA and were significantly reduced compared with both young and old rats thereafter. Urinary potassium concentrations differed between young and old rats only on the first 2 days of DOCA administration.

Table 1. One-day changes in body water and electrolyte balance measures from the last day of baseline to the first day of doxycorticosterone treatment in young (5 mo), middle-aged (12 mo), and old (30 mo) rats

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<th>ΔUrine Volume, ml</th>
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Values are means ± SE. Body weight-adjusted values are in ml or μmol/100 g body wt. Young and old rats did not differ on any of the measures. *Significantly different from both the other groups (main effect of age, $P < 0.05$). †Significantly different from young rats (main effect of age, $P < 0.05$).
BW-adjusted urinary sodium excretions and sodium balances were not different between the ages during baseline and increased significantly for all ages during DOCA (Fig. 5). In response to DOCA, middle-aged rats had significantly higher urinary sodium excretions than the other groups beginning the first day of treatment (Age × Days interaction, $F_{20,150} = 8.93; P < 0.001$). In addition, young rats excreted significantly more sodium than old rats by the third day of DOCA. During DOCA, middle-aged rats had significantly higher BW-adjusted sodium balances compared with old rats on most days and compared with young rats on the last day of treatment (Age × Days interaction, $F_{20,150} = 2.55; P < 0.01$). Young and old rats had significantly increased sodium balances only on the last days of DOCA. BW-adjusted urinary potassium excretions were significantly higher for old rats compared with both young and middle-aged rats during baseline (Age × Days interaction, $F_{20,150} = 4.00; P < 0.001$). In response to DOCA, urinary potassium excretions increased slightly but significantly for young and middle-aged rats, and decreased slightly but significantly for old rats.

Effects of DOCA on the first day of treatment. As a measure of the initial effects of DOCA, we analyzed the differences (i.e., change scores) in water and sodium intakes and excretions between the last day of baseline and the first day of DOCA treatment. For example, the changes in total fluid intake (i.e., the additional amounts of fluid consumed) on the first day of DOCA compared with the day before were equivalent between groups (Table 1). However, the changes in urine volume (i.e., the additional urine volumes) on the first day of DOCA were significantly greater for middle-aged rats compared with both other groups, on an absolute or BW basis (both $F_{2,15}$ values $\geq 5.91; P < 0.05$). As a result, middle-aged rats

On an absolute basis, urinary sodium excretions and sodium balances during baseline did not differ between ages and increased significantly for all ages during DOCA (Age × Days interactions, both $F_{20,150}$ values $\geq 2.82; P < 0.001$). During DOCA, middle-aged rats consistently had higher sodium excretions compared with both young and old rats while young rats had higher sodium excretions than old rats only on some days. Urinary potassium excretions were significantly higher for old rats compared with the other groups during baseline (Age × Days interaction, $F_{20,150} = 3.95; P < 0.001$). Young and middle-aged rats had significantly higher levels of urinary potassium excretion compared with baseline values on most days of DOCA treatment.

Fig. 3. BW-adjusted daily total fluid intakes, urine volumes, water balances (Wat Bal), and change (Δ) in relative water balances for young (5 mo), middle-aged (12 mo), and old (30 mo) rats during treatment with DOCA. For each age group the change in water balance is from their respective average water balance over 3 days of baseline. All groups had significantly increased total fluid intakes and urine volumes during DOCA treatment compared with baseline values. There were significant age-related differences in total fluid intakes and urine volumes during DOCA treatment. Water balances were significantly higher on the first day of DOCA compared with all other days. Young rats had significantly higher water balances than the other groups on the first day of DOCA treatment. Total fluid intake = water + saline. Values are means ± SE. *Significantly different from both the other groups, $P < 0.05$.

Fig. 4. Daily urinary sodium (UNa) and potassium (UK) concentrations for young (5 mo), middle-aged (12 mo), and old (30 mo) rats during treatment with DOCA. All groups had significantly increased UNa and significantly decreased UK during DOCA treatment compared with baseline values. There were significant age-related differences in UNa and UK both during baseline and during DOCA treatment. Values are means ± SE. *Significantly different from both the other groups, $P < 0.05$. *Significantly different from both the other groups, $P < 0.05$. 

had the smallest increases in water balances on the first day of DOCA on either analysis (both $F_{2,15}$ values = 4.91; $P < 0.05$). As noted above, middle-aged rats drank more saline solution on the first day of DOCA than the other groups. However, the changes in saline intake (i.e., the additional amount of sodium consumed compared with the day before) did not differ between groups. Nevertheless, middle-aged rats excreted significantly more of the additional ingested sodium on the first day of DOCA than the other groups on either an absolute or BW basis (both $F_{2,15}$ values = 8.06; $P < 0.05$) and the changes in sodium balances on the first day of DOCA were significantly less for middle-aged rats on a BW basis ($F_{2,15} = 5.60; P < 0.05$). The changes in BW on the first day of DOCA were equivalent across the ages on either an absolute or BW basis. The results for young and old rats did not differ on any of these measures.

**DISCUSSION**

This experiment examined the effects of age on water and sodium intakes, excretions, and balances in response to daily administration of DOCA to male BN rats. As expected, we found age-related differences in salt appetite responses. However, “middle-aged” adult (12 mo), and not young (4 mo), rats had the highest sodium intakes in response to DOCA. In addition, old (30 mo) rats had a strikingly robust salt appetite response to DOCA, which contrasts markedly with their nearly absent lack of salt appetite response to sodium depletion. Although no definitive mechanism for the age differences in salt appetite was determined, the present work produced evidence consistent with roles for age differences in renal handling of water and sodium and, possibly, sodium taste.

The highest daily intakes of concentrated saline solution in response to DOCA were by middle-aged adult rats. Middle-aged rats drank nearly twice as much saline solution daily as did young rats and threefold more than did old rats. This finding differs considerably from observations of age-related declines in thirst for male BN rats. In response to several dipsogenic stimuli and taking BW into account, we find that young rats drink the most followed in descending order by middle-aged and old rats, although middle-aged rats sometimes drink no more than do old rats (44, 45, 47). Mineralocorticoids produce sodium ingestion by actions at central MRs either to directly stimulate salt appetite (14, 35, 36) or to reduce activity within a central system that inhibits salt appetite (41). The greater salt appetite response of middle-aged rats seems unlikely to be directly related to numbers or affinity of central MRs as these are at their highest levels in young rats (i.e., 3–5 mo) and only decline thereafter (15, 26, 33, 49, 53). However, age-related effects on MR number and affinity specifically within brain areas associated with the control of salt appetite (e.g., amygdala, circumventricular organs) have not been reported. Another possibility is that salt appetite-related neural mechanisms located “downstream” from central MRs are augmented in middle-aged rats.

Middle-aged rats had higher preference for saline solution under baseline conditions compared with the other groups, which is consistent with the possibility of increased avidity for salty taste before treatment (Fig. 2). With the start of DOCA treatment, the saline intakes and saline preference ratios increased for all groups and remained highest for middle-aged rats throughout testing. Middle-aged rats consumed most of their daily fluid intakes as saline beginning the first day of treatment. The daily mixture of ingested water and saline stabilized by 3–4 days of treatment, yielding peak concentrations of hypertonic saline “cocktail” consumed at each age: young, ~1.4% NaCl, middle-aged, ~1.6% NaCl, and old, ~1.1% NaCl. There are limited data on age-related changes in sodium preference or rejection thresholds for rats—rarely into old age—and the available data suggest minimal changes in sodium taste function with advanced age (11, 22, 23, 32, 42). As a caveat, we note that these prior preference studies used rats maintained on standard diet while rats in the present work were maintained on sodium-deficient diet.

As an index of acute responses to DOCA, we used changes in levels of several variables from the first day of DOCA and the preceding day and found significant age differences in urinary handling of water and sodium (Table 1). For example, despite the groups ingesting similar, additional amounts of fluid (i.e., water + saline) on the first day of DOCA, urine volumes increased significantly more, and resulting water balances increased significantly less, for middle-aged rats compared with the other groups. Similarly, while the additional amounts of sodium consumed on the first day of DOCA compared with the preceding day did not differ between groups, middle-aged rats excreted more sodium than did the
other groups, so that the sodium balances did not increase as much for middle-aged rats as for the other groups. These results suggest that middle-aged rats compensated for the additional ingestion of water and sodium on the first day of DOCA by excreting relatively more of both substances than did young and old rats. Thus middle-aged rats had a relatively higher turnover of water and sodium, which may have permitted them to continue drinking larger amounts of both.

Old rats had a substantial salt appetite response to daily administration of DOCA. The average intakes of concentrated saline solution by old rats increased from <1 ml/day during baseline to >26 ml/day during DOCA treatment. These intakes make the salt appetite response of old rats as robust as that of young rats on an absolute basis. The finding that old BN rats express salt appetite at all is both novel and noteworthy. Prior work shows that old BN rats almost completely lack depletion-induced salt appetite (5, 48) even after multiple sodium depletions (48) and fail to increase sodium intake in response to chronic administration of low doses of angiotensin-converting enzyme inhibitor (32, 48). We speculate that one contributing factor to the diminished salt appetite, and also thirst, of old rats in experimental studies is the ability to endogenously produce the relevant dipsogenic or natriuretic stimulus, e.g., a hormone. For example, the profound inability of old animals to release renin may explain their refractory drinking and sodium appetite. The finding that old BN rats express salt appetite at all is both novel and noteworthy. Prior work shows that old BN rats almost completely lack depletion-induced salt appetite (5, 48) even after multiple sodium depletions (48) and fail to increase sodium intake in response to chronic administration of low doses of angiotensin-converting enzyme inhibitor (32, 48). We speculate that one contributing factor to the diminished salt appetite, and also thirst, of old rats in experimental studies is the ability to endogenously produce the relevant dipsogenic or natriurexic stimulus, e.g., a hormone. For example, the profound inability of old animals to release renin may explain their refractory drinking and sodium appetite.

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Perspectives and Significance

The present results provide an important demonstration that very old, possibly senescent, rats are capable of expressing robust salt appetite behavior in response to administration of a powerful mineralocorticoid compound. These findings mean that diminished sodium ingestion by elderly rats in other experimental situations is not due to a general inability to respond. Rather, just as distinct mechanisms for producing thirst (i.e., osmotic vs. renin-dependent) appear to decline with age at different rates (25, 44), so might different mechanisms for producing salt appetite. For example, the failure of old rats to adequately ingest sodium following sodium depletion now appears to be due to the loss of a critical mechanism for producing salt appetite, namely, the ability to secrete renin, and not to the inability per se to express salt appetite. The observation that middle-aged rats drank far more sodium solution than did young rats may have interesting developmental implications. For example, mineralocorticoid-induced salt appetite may mature later in life than do the various kinds of thirsts more robustly expressed by young animals.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

Author contributions: R.L.T. conception and design of research; R.L.T. and T.G.B. performed experiments; R.L.T. analyzed data; R.L.T. and A.K.J. interpreted results of experiments; R.L.T. prepared figures; R.L.T. drafted manuscript; R.L.T. and A.K.J. edited and revised manuscript; R.L.T., T.G.B., and A.K.J. approved final version of manuscript.

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