Disruption of the Type 2 Dopamine Receptor Gene Causes a Sodium-Dependent Increase in Blood Pressure in Mice

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Background: Dopamine D_2 receptors (D_2Rs) are expressed in the kidney. It has not been determined whether D_2Rs are involved in the mechanism of sodium handling and blood pressure (BP) control.

Methods: The function of D_2Rs was investigated in mice disrupted with D_2R gene (D_2KO mice). Six-week-old male D_2KO mice and wild-type (WT) mice were fed high-salt (4% NaCl) or low-salt (0.01% NaCl) diets for 8 weeks.

Results: Before starting the metabolic diet, there were no significant differences in body weight, food consumption, and 24-h urine excretions of creatinine, sodium and potassium. The high-salt diet caused a significant elevation in systolic BP in D_2KO mice but not in WT mice. Calculation of sodium and potassium balances revealed a significantly high level of sodium retention in D_2KO mice placed on the high-salt diet. Twenty-four-hour urine norepinephrine excretions and heart rates, indicators of sympathetic activity, were not different in D_2KO and WT mice on the high-salt diet. Administration of nemonapride, a specific D_2-like receptor antagonist, to WT mice given 0.9% NaCl in drinking water caused suppression of urinary sodium excretion but had no effect in mice without salt loading.

Conclusions: These results suggest that D_2 receptors promote sodium excretion during a period of high salt intake. A defect in this mechanism may result in sodium-dependent BP elevation. Am J Hypertens 2003;16: 853–858 © 2003 American Journal of Hypertension, Ltd.

Key Words: Dopamine, knockout, receptor, blood pressure, sodium.

Intrarenally produced dopamine plays an important role in the regulation of renal sodium excretion. The dopamine-induced natriuretic mechanism is activated during high salt intake, and attenuated dopamine-induced natriuresis is thought to be involved in the mechanism of salt sensitivity in blood pressure (BP).[1–3]

Dopamine receptors are classified into two major families: D_1-like receptors, which include D_1 and D_5 subtypes; and D_2-like receptors, which include D_2, D_3, and D_4 receptors.[4] Both D_1-like and D_2-like receptors are present in the kidney.[1–3,5] Although it is well established that D_1-like receptors mainly mediate the dopamine-induced natriuresis,[2,3] the roles of D_2-like receptors, independent of D_1-like receptors, in renal tubular and vascular functions are not clear. Results of in vitro experiments have suggested that D_2-like receptors are necessary to potentiate the D_1-like receptor–induced natriuresis in renal tubular cells.[6,7] However, in vivo studies designed to investigate this hypothesis using pharmacologic agents have shown conflicting results.[8,9] Although antagonists for D_2-like receptors are widely used as antipsychotic agents, there has been little investigation of their effects on the kidney.

The present study was designed to investigate the role of D_2Rs in the homeostatic control of sodium balance and BP using mice disrupted with D_2R gene. The effects of nemonapride, a D_2-like receptor antagonist, on sodium balance were also investigated to determine whether the observations in the knockout mice have clinical relevance.

Received July 26, 2002. First decision November 1, 2002. Accepted June 3, 2003.

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This work was supported by grants-in aid for scientific research (11771511, 13470521, and 14572183) from the Ministry of Education, Japan, and by a grant from the Charitable Trust Clinical Pathology Research Foundation of Japan.

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0895-7061/03/$30.00
doi:10.1016/S0895-7061(01)01013-6

Methods

D_2 Knockout Mice

The generation of D_2 receptor-knockout mice (C57/BL) has been described previously.[10] These knockout mice lack both the $D_{2\ long}$ and $D_{2\ short}$ subclasses of the D_2 receptor. Mice homozygous (−/−) for the deleted D_2 receptor gene and wild-type (+/+) mice, produced by intermating heterozygous (+/−) mice, were used in this study. Hiroshima University Committee for DNA Recombinant Experiments approved all of the experiments.

Sodium Balance Study

Male homozygous mutant mice (D_2KO mice) at 6 weeks of age, and age- and sex-matched wild-type (WT) mice, were divided into two groups for each strain and fed a high-salt diet containing 4% NaCl or a low-salt diet containing 0.01% NaCl for 8 weeks. The contents of potassium (0.36%), calcium, protein, and carbohydrates in the two diets were identical. Before starting the high- or low-salt diet, all mice were fed normal mouse chow containing 0.1% NaCl.

Systolic BP and heart rates were measured before and at 2, 4, and 8 weeks after starting the diet in conscious mice (each group, $n = 6$ to 8 by the tail-cuff method as previously described[11] (BP98, Softron, Tokyo, Japan). For each mouse BP was measured five times and averaged. The coefficient of variance of the averaged BP on 3 consecutive days (day-to-day variation) was 2.3% ± 1.7% (mean ± SD, $n = 7$). Blood pressures measured by the tail-cuff method were significantly correlated with those measured by the direct method ($r^2 = 0.80$, $P < .01$, $n = 8$).

Consumption of metabolic diet and drinking water, 24-h urine volume, and 24-h excretions of sodium and potassium were determined using metabolic cages (Nalgene). Sodium and potassium balances were then calculated from the chow intakes and the urine excretions. Twenty-four-hour urine excretions of free norepinephrine (NE) and free dopamine (DA), as indicators of systemic sympathetic activity and renal local DA production, respectively, were determined in another cohort of mice (each group, $n = 18$) in weeks 4 and 8. Twenty-four-hour urine excretion of free DA is highly correlated with the amount of DA locally produced within the kidney.[12] Assays for catecholamines in the urine were performed as previously described[13] using high-performance liquid chromatography with electrochemical detection. To obtain a sufficient amount of urine, 24-h urine was collected from three mice placed together in a metabolic cage, and the urine from the three mice was regarded as one sample in the statistical analysis.

Next we investigated the effects of nemonapride, a specific D_2-like receptor antagonist, on urinary sodium excretion in another cohort of WT mice ($n = 12$). Mice were given a bolus subcutaneous administration of nemonapride (gift from Yamanouchi Pharmaceutical Co, Tokyo, Japan) at 1 mg/kg body weight,[14] and 24-h urine collection was started after the nemonapride injection to determine levels of sodium, potassium, and creatinine urine excretion. The basal values of 24-h electrolyte and creatinine excretions were obtained before or 2 days after the day of nemonapride infusion in a cross-over design. Fractional excretion of sodium (FENa) was calculated as follows: [urine sodium concentration] × [serum creatinine concentration]/[serum sodium concentration] × [urine creatinine concentration]. The same procedure was repeated while the mice were given 0.9% NaCl in drinking water. As a control for nemonapride, the same experiment was performed using quinpirol, a specific D_2-like receptor agonist, at a dose of 5 mg/kg.

Table 1. Baseline characteristics of 6-week-old D_2 receptor knockout mice (D_2KO) and wild-type control mice (WT)

Characteristic	WT	D_2KO
Body weight (g)	22.0 ± 0.40	21.9 ± 0.44
Systolic blood pressure (mm Hg)	108.6 ± 2.2	103.6 ± 3.9*
Heart rate (beats/min)	527.0 ± 20	533 ± 16
Water and chow intake		
Chow (g/day)	0.80 ± 0.14	0.81 ± 0.23
Water (mL/day)	1.27 ± 0.34	1.15 ± 0.22
Urine output (m/day)	0.95 ± 0.09	0.74 ± 0.06
24-h Urine Cr excretion (g/day)	333 ± 10	282 ± 20
24-h Urine Na excretion (Eq/mgCr)	359 ± 21	367 ± 22
24-h Urine K excretion (Eq/mgCr)	546 ± 35	655 ± 66

* $P < 0.05$ *v* WT.
Values are mean ±SEM, $n = 10$ each strain.
Cr = creatinine; Na = sodium; K = potassium.

Statistical Analysis

All data are expressed as means ± SEM. Comparison between D_2KO and WT mice was made using the unpaired Student *t* test. Comparisons among the four groups were made using analysis of variance combined with the Scheffé test. A value of $P < .05$ was accepted as statistically significant.

Results

Sodium and Potassium Balance, Body Weight, and BP During the Metabolic Study

Before starting the high- or low-salt diets, there were no significant differences in body weight, heart rate, food and water consumption, or urinary excretions of sodium, potassium, and creatinine between the D_2KO mice and WT mice (Table 1).

Table 2 shows the results of the balance study. Water intake and urine volume of D_2KO mice placed on high-salt

Table 2. Sodium (Na) and potassium (K) balance in wild-type (WT), and D_2 receptor knockout (D_2KO) mice during the diet protocol.

	WT		D_2KO	
	Low Salt	**High Salt**	**Low Salt**	**High Salt**
2-Week				
Water intake (mL/day)	2.2 ± 0.6	2.7 ± 0.4	1.9 ± 0.4	1.4 ± 0.3*
Urine volume (mL/day)	1.1 ± 0.2	1.5 ± 0.2	0.8 ± 0.1	1.0 ± 0.1*
Na intake (μEq/day)	17 ± 3	631 ± 72†	15 ± 2	539 ± 71†
Na excretion (μEq/day)	19 ± 3	551 ± 91†	11 ± 2	349 ± 30†‡
N balance (μEq/day)	−2 ± 4	80 ± 32	4 ± 1	191 ± 65†‡
K intake (μEq/day)	127 ± 21	116 ± 13	113 ± 16	99 ± 13
K excretion (μEq/day)	120 ± 18	113 ± 16	100 ± 6	85 ± 5
K balance (μEq/day)	6 ± 24	4 ± 13	12 ± 13	14 ± 10
4-Week				
Water intake (mL/day)	2.0 ± 0.4	2.0 ± 0.5	1.7 ± 0.3	0.8 ± 0.2*
Urine volume (mL/day)	1.0 ± 0.2	1.4 ± 0.3	0.6 ± 0.1	0.6 ± 0.1*
Na intake (μEq/day)	14 ± 5	541 ± 22†	18 ± 3	448 ± 93†
Na excretion (μEq/day)	17 ± 5	514 ± 227†	14 ± 3	337 ± 59*†
Na balance (μEq/day)	−4 ± 7	27 ± 67	6 ± 2	111 ± 48§
K intake (μEq/day)	121 ± 39	100 ± 41	133 ± 21	82 ± 19
K excretion (μEq/day)	116 ± 14	93 ± 13§	122 ± 12	86 ± 11§
K balance (μEq/day)	13 ± 34	1 ± 17	37 ± 16	5 ± 12
8-Week				
Water intake (mL/day)	2.0 ± 0.5	1.2 ± 0.3	1.5 ± 0.2	1.1 ± 0.5
Urine Volume (mL/day)	1.8 ± 0.5	1.5 ± 0.2	0.5 ± 0.1	0.9 ± 0.20
Na intake (μEq/day)	18 ± 4	424 ± 156†	12 ± 3	399 ± 86†
Na excretion (μEq/day)	20 ± 7	461 ± 76†	8 ± 2	311 ± 54*†
Na balance (μEq/day)	−1 ± 6	−37 ± 119	3 ± 3	88 ± 39
K intake (μEq/day)	140 ± 31	79 ± 25	104 ± 17	73 ± 14
K excretion (μEq/day)	100 ± 23	40 ± 23	76 ± 12	68 ± 12
K balance (μEq/day)	36 ± 19	28 ± 8	28 ± 21	20 ± 9

Values are mean ± SEM (n = 6).
* $P < .05$, † $P < .01$ *v* low salt diet group in the same strain, ‡ $P < .01$ *v*, high salt diet group of WT mice.
§ $P < .05$.

diet were significantly less in weeks 2 and 4 than those of WT mice on the same diet. In addition, D_2KO mice tended to consume a smaller amount of the high-salt diet than did WT mice, indicating that the behavior of D_2KO mice related to drinking and eating is different from that of WT mice. However, calculation of sodium and potassium balances revealed a significantly larger retention of sodium, but not potassium, in D_2KO mice on the high-salt diet than in WT mice on the same diet. There was no difference between the sodium or potassium balance in D_2KO and WT mice placed on the low-salt diet throughout the experimental period. As the body weight of D_2KO mice was slightly less than that of WT mice before the start of the experiment, the increase in body weight in D_2KO mice during the experimental period tended to be larger than in WT mice. However, statistical analysis showed that there was no significant difference between the body weights of D_2KO and WT mice throughout the experimental period, although mice on the high-salt diet, regardless of strain, were heavier than those on the low-salt diet. Interestingly, systolic BP, which was slightly but significantly lower in D_2KO mice than in WT mice before starting the metabolic diet (Table 1), gradually increased in D_2KO mice on the high-salt diet (Fig. 1b), and in week 8, the BP of D_2KO mice was significantly higher than that of WT mice on the same diet. On the other hand, a high-salt diet for 8 weeks had no significant effect on systolic BP in WT mice. Heart rate tended to increase during the period of high salt intake in both D_2KO and WT mice, but there was no significant difference between heart rates in the two strains of mice on the same diet (Fig. 1c).

Twenty-Four-Hour Urine Excretions of Catecholamines

Twenty-four-hour urine NE excretion was significantly greater in D_2KO mice than in WT mice during the period in which the mice were fed a low-salt diet (Fig. 2, upper panel), indicating that NE release from sympathetic nerve endings was enhanced, probably because of the deficit of D_2R in prejunctional sympathetic nerve ganglia.[15] However, the 24-h urine NE excretion in D_2KO mice was decreased by increasing the salt intake, and the amounts of NE excretion in D_2KO and WT mice during the high-salt diet period were similar, indicating that a heightened sympathetic tone (if any) is unlikely to explain the high-salt diet-induced changes in sodium balance and BP in D_2KO mice. The DA excretions in 24-h urine, as an index of

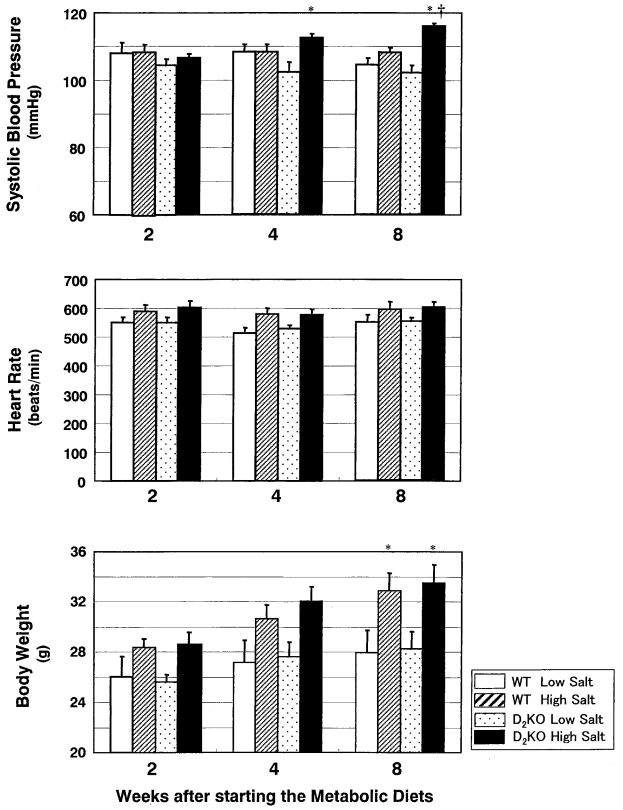

FIG. 1. Effects of high-salt or low-salt diet on body weight (**a**), tail-cuff systolic blood pressure (**b**), and heart rate (**c**) in D_2 receptor knockout (D_2KO) and wild-type (WT) mice. Note that high salt intake caused significant elevation only in D_2KO mice. Values are means ± SEM. *$P < .05$ *v* mice of the same strain on a low-salt diet; †$P < .05$ *v* WT mice on the same diet.

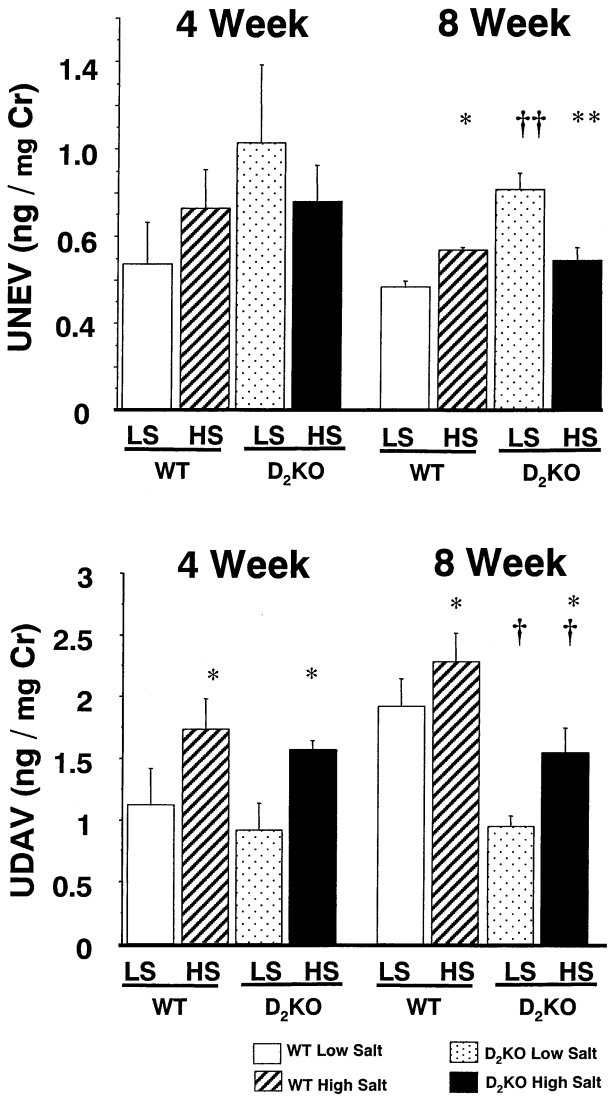

FIG. 2. (**Upper panel**) Effects of high-salt (HS) or low-salt (LS) diet on 24-h urine excretions of norepinephrine (UNEV) in D_2 receptor knockout (D_2KO) and wild-type (WT) mice. In D_2KO mice the NE excretion is increased during LS diet, whereas it is increased during HS diet in WT mice. (**Lower panel**) Effects of high-salt (HS) or low-salt (LS) diet on 24-h urine excretions of free dopamine (UDAV) in D_2 receptor knockout (D_2KO) and wild-type (WT) mice. Dopamine excretion was enhanced by the HS diet both in WT mice and D_2KO mice. Values are means ± SEM. Data are corrected by 24-h creatinine excretion. **$P < .01$, *$P < .05$ *v* mice of the same strain on a low-salt diet, ††$P < .01$ *v* WT mice on the same diet. The number of mice is 18 each group, but the number of samples is six each group, as three mice were needed to obtain one 24-h urine sample.

renal local dopamine production, were greater in mice fed the high-salt diet than in those fed the low-salt diet regardless of mouse strain (Fig. 2, lower panel), indicating that the dopamine-mediated natriuretic mechanism was normally activated by a high salt intake in both D_2KO and WT mice. Interestingly, DA excretion was significantly less in D_2KO mice than in WT mice during the high-salt and low-salt diet periods.

At the end of the experimental period, there was no difference in either creatinine clearance or renal mass among the four groups (Table 3), thus ruling out the possibility that changes in excretions of electrolyte and catecholamines in 24-h urine reflect changes in glomerular filtration rate.

Effects of Nenonapride and Quinpirole Administration

Nenonapride and quinpirole had no significant effect on 24-h excretions of sodium, potassium, creatinine, and NE in mice that were fed normal sodium (0.1% NaCl) diet. However, nenonapride significantly reduced sodium excretion in 24-h urine when mice were sodium loaded. On the other hand, quinpirole treatment in sodium-loaded mice caused increases in both sodium intake and sodium excretion (Table 4). However, a rate of excreted sodium relative to the intake was approximately 95% in quinpirole-treated mice compared with only 70% in nontreated mice ($P < .05$). Furthermore, FENa was significantly greater in quinpirole-treated mice than in nontreated mice, indicating that the increase in sodium excretion in quinpirole-treated mice was, at least in part, attributable to a renal tubular mechanism and not a simple reflection of increased sodium load. Taken together, these results suggest that D_2-like receptors is involved in the mechanism of

Table 3. Creatinine clearance and renal mass at the end of the 8-week diet protocol

Characteristic	WT Mice		D_2KO Mice	
	Low Salt	High Salt	Low Salt	High Salt
Body weight (g)	26.7 ± 0.7	29.8 ± 0.6	25.2 ± 1.3	29.2 ± 0.2
Serum creatinine concentration (mg/dL)	0.11 ± 0.02	0.13 ± 0.03	0.13 ± 0.03	0.14 ± 0.01
24-h-Urine creatinine excretion (mg/day)	0.22 ± 0.09	0.22 ± 0.03	0.23 ± 0.06	0.26 ± 0.06
Creatine clearance (μL/min)	138 ± 50	118 ± 26	122 ± 74	129 ± 9
Renal mass (mg)	245.9 ± 13	231.7 ± 11	225.6 ± 10	241.7 ± 12

Values are mean ± SEM (n = 5). Data are obtained in separate groups of mice from those shown in Table 2.

rejection of a sodium load. Blood pressure was not altered by nemonapride, quinpirole, or sodium loading.

Discussion

In the present study, we demonstrated that mice without D_2Rs displayed an impaired ability to excrete an excessive sodium intake, resulting in a significantly high level of sodium retention and sodium-sensitive elevation in BP. Interestingly, the D_2R mediated modulation of sodium excretion had a significant impact on total body sodium balance specifically during high sodium but not low sodium intake. These results indicate that D_2R is involved in the mechanism for natriuretic response to sodium loading, and that D_2R is one of the key factors that determine the sodium sensitivity of BP.

An increase in renal local dopamine production is one of the most important natriuretic mechanisms activated in response to high sodium intake.[16,17] In D_2KO mice, urinary free DA excretion, which reflects renal local DA production,[12] was significantly less than in WT mice, indicating that insufficient DA-induced natriuresis during high salt intake may have been partly responsible for the sodium retention in D_2KO mice. Consistent with our observations, reduced urinary dopamine excretion during high sodium intake has been reported in certain subsets within patients with salt-sensitive essential hypertension (eg, nonmodulating hypertension).[18]

It is notable that WT mice were able to adjust the sodium excretion to achieve negative sodium balance in 8 weeks; this seems to indicate a subacute modulation of steady-state sodium excretion that involves a number of natriuretic mechanisms including renin-angiotensin system, sympathetic system, and dopamine system. In D_2KO mice, such a modulation was incomplete and slow. D_2KO mice retained significantly greater amounts of sodium than

Table 4. Effects of nemonapride and quinpirole on urine volume and urinary sodium and potassium excretions of mice in normal and sodium-loaded state.

Characteristic	Normal NaCl Intake (*n* = 6)		High NaCl Intake (*n* = 12)	
	Nemonapride (−)	Nemonapride (+)	Nemonapride (−)	Nemonapride (+)
Water intake (mL/day)	2.36 ± 0.4	1.79 ± 0.5	2.01 ± 0.6	1.37 ± 0.3
Urine volume (mL/day)	0.96 ± 0.1	0.99 ± 0.2	1.31 ± 0.2	1.26 ± 0.2
UCrV (μg/day)	223.6 ± 39	228.4 ± 24	263.3 ± 67	255.7 ± 44
Na intake (μEq/day)	82 ± 5	96 ± 6	376 ± 190	313 ± 45
UNaV (μEq/day)	69.5 ± 12	74.6 ± 8	226.1 ± 77	141.9 ± 22*
FENa (%)	0.65 ± 0.3	0.67 ± 0.3	0.86 ± 0.2	0.58 ± 0.3*
UKV (μEq/day)	160.9 ± 32	115.5 ± 11	142.7 ± 27	144.6 ± 42
Characteristic	**Normal NaCl Intake (*n* = 6)**		**High NaCl Intake (*n* = 12)**	
	quinpirole (−)	**quinpirole (+)**	**Quinpirole (−)**	**Quinpirole (+)**
Water intake (mL/day)	1.85 ± 0.2	1.46 ± 0.4	2.83 ± 0.4†	4.72 ± 1.2†*
Urine volume (mL/day)	1.16 ± 0.2	1.00 ± 0.1	2.10 ± 0.2†	4.26 ± 0.4†
UCrV (μEq/day)	220 ± 47	225 ± 25	340 ± 20†	380 ± 11†
Na intake (μEq/day)	122 ± 5	114 ± 8	446 ± 18†	732 ± 62†*
UNaV (μEq/day)	95 ± 14	72 ± 15	316 ± 17†	696 ± 66†*
FENa (%)	0.6 ± 0.1	0.48 ± 0.1	1.02 ± 0.2†	1.97 ± 0.5†*
UKV (μEq/day)	158 ± 66	171 ± 26	243 ± 13	220 ± 7

Values are mean ± SEM.

* $P < .01$ *v* mice on high NaCl intake and nemonapride (−) or quinpirole (−).

† $P < .05$ *v* mice on normal NaCl groups.

did WT mice in the first 2 weeks, although the extent of sodium retention decreased thereafter. Blood pressure rose after week 4, which may have induced a pressure-natriuresis, thereby partially compensating the sodium retention in D_2KO mice. As a result, body weights of D_2KO mice on high salt diet did not markedly increase despite the sodium retention.

Dopamine receptors in renal tubules play a central role in the regulation of tubular sodium reabsorption. The D_2Rs are expressed in the renal tubules.[5] Therefore, it is thought that the sodium retention in D_2KO mice was caused by the loss of function of D_2Rs in the renal tubules. However, functional D_2Rs are present not only in renal tubules but also in the brain, presynaptic sympathetic ganglia,[15] adrenal gland,[19] and renal and systemic resistant arteries.[20] Based on the data of 24-h urine NE excretion, D_2KO mice on the low-salt diet may have had heightened sympathetic tone. However, the decreased NE excretion during high-salt diet period may indicate suppression of sympathetic tone whereas sodium was retained and BP was elevated, excluding the possibility that the sympathetic activation is primarily responsible for the high-salt induced changes in sodium balance and BP. Heart rate, another indicator of sympathetic activity, in D_2KO mice was not different from that in WT mice throughout the experimental period. D_2-like receptors in the adrenal cortex have been reported to inhibit aldosterone secretion.[19] Based on the results regarding potassium balance in the present study (Table 2), the activities of aldosterone in D_2KO and WT mice do not seem to be different. These measurements of catecholamine, heart rate, and potassium balance may collectively support a thesis that the sodium retention and salt sensitive elevation in BP in D_2KO mice is mediated by renal tubular mechanism. However, these measures are only suggestive, and further investigations are needed. The precise mechanisms whereby the lack of D_2R caused sodium retention and salt-sensitive BP elevation remains to be determined.

Consistent with the observations in D_2KO mice, a blockade of D_2-like receptors by nemonapride mimicked the effect of D_2R-knockout on sodium excretion during the period of high-salt intake. Unfortunately, administration of quinpirole, a D_2-like receptor agonist, increased not only sodium excretion but also sodium intake, probably because of its effect on central nervous system, thereby confounding interpretation of the renal effect. However, data for FENa and rate of sodium intake and excretion support the notion that stimulation of D_2-like receptor causes natriuresis.

In summary, we have demonstrated that D_2R play a significant role in sodium excretion in response to sodium loading and that a defect in this system may be a cause of sodium-sensitive hypertension. When we use D_2-like receptor antagonists as antipsychotic agents, we need to be careful with regard to induction of sodium-sensitive hypertension.

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