

Acute influence of sodium valproate on sodium and chloride urinary excretion in rats

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There is increasing evidence indicating that certain drugs evoke adverse drug effects that depend on the gender of patients. Elucidation of gender-effect of various drugs by means of preclinical trials is an important field of pharmacology. The chloriuretic and natriuretic effect of valproates (VPA) had not been investigated earlier, so the aim of the present study was to define peculiarities of 24-h urinary sodium (Na) and chloride (Cl) excretion in young adult Wistar rats of both genders and to evaluate the influence of sodium valproate (VPA). We measured 24-h urinary Na, Cl, creatinine and pH levels. Twenty-eight control intact Wistar rats (14 males and 14 females) and 26 Wistar rats (13 males and 13 females) were investigated after a single intragastric administration of 300 mg/kg VPA.

In control intact Wistar rats, 24-h diuresis per 100 g of body weight, 24-h urinary Na excretion per 100 g of body weight and Na/Cl ratio in female rats were found significantly higher than in male rats. After a single administration of VPA, total 24-h diuresis and 24-h diuresis per 100 g of body weight were significantly higher in VPA rats of both genders. 24-h urine Na levels, 24-h urine Na excretion, 24-h urinary Na excretion per 100 g of body weight and the Na/creatinine ratio were significantly higher in VPA-male and VPA-female rats than in gender-matched controls. The 24-h urinary Cl excretion, 24-h urinary Cl excretion per 100 g of body weight and the Cl/creatinine ratio were found significantly higher in VPA-male than in VPA-female rats.

These data show that VPA, alongside the diuretic effect, enhances Na and Cl excretion with urine. 24-h natriuretic and chloriduretic response to VPA in male rats was significantly higher than in female rats. The mechanism of such gender-related effect is not clear.

Key words: valproate, sodium, chloride, urine, rats, gender

INTRODUCTION

There is increasing evidence indicating that certain drugs evoke adverse drug effects that depend on the gender of patients. Hyponatremia due to sodium valproate (VPA) was reported (1, 2). Our data revealed gender-related differences in chloride (Cl) transport across the cell membrane, intracellular Cl level and the sensitivity of Cl efflux to vasopressine in smooth muscle cells of rats (3). Therefore, elucidation of gender-effect of various drugs by means of preclinical investigations is an important field of pharmacology.

Na and Cl channels have a critical role in the functioning of the nervous system by asserting con-

trol over the voltage potentials across the plasma membrane (4). The voltage-gated Na channels (nicotinic acetylcholine receptor, AMPA and KA glutamate receptor) are the target of most of the classical (among them VPA) and new antiepileptic drugs (5). The γ -aminobutyric acid type A receptor (GABAA) is an ionotropic receptor whose subunits form a functional Cl channel (6, 7). The Cl channel of the GABAA receptor is rapidly activated by VPA (5).

The chloriuretic and natriuretic effect of VPA had not been investigated earlier, so the aim of the present study was to evaluate the influence of VPA on urine sodium (Na) and Cl excretion in Wistar rats of both genders.

MATERIALS AND METHODS

Twenty-eight Wistar control intact rats (14 males and 14 females), 26 Wistar rats (13 males and 13 females) were

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examined after a single intragastric administration of 300 mg/kg sodium valproate (Convulex, 300 mg/ml, drops, Gerot Pharmazeutika Wien, Austria) (VPA rats). The experiment was performed in 2004–2005.

The experiment was carried out on age-matched male and female rats. The mean age of control rats was 91 ± 9 days for males and 90 ± 8 days for females. The mean age of VPA rats was 97 ± 10 days for males and 95 ± 9 days for females. The mean weight of male rats was 283 ± 30 g in control and 298 ± 23 g in VPA. The mean weight of female rats was 236 ± 18 g in control and 240 ± 16 g in VPA. The weight was significantly higher in male than in female rats in all groups ($p < 0.05$).

The animals were housed in standard colony cages with free access to food (chow pellets) and tap water. The room temperature was 21 ± 1 °C. The rats were on a natural light-dark cycle. All experiments were performed according to the institutional guidelines for animal care in order to avoid any unnecessary distress to the animals and to reduce the number of animals used. The animals were housed in described conditions and acclimated for at least 5 days before experiments. 24-h urine was collected holding a rat alone in a special diuresis cage (diure-

sis cage for rats 3700D000/3701D000, Tecniplast, Italy) for 24 h (from 9:00 a.m. till 9:00 a.m. of the next day) with free access to tap water, without food, in the same temperature and light conditions.

24-h urinary sodium (Na) and chloride (Cl) levels were analyzed with an EML-105 electrolyte analyzer (Radiometer, Denmark). Urinary pH levels were measured with a pH/mV/ion meter (ION Meter pH 340/ION, Germany).

We calculated the 24-h excretion of Na, Cl and creatinine, the Na/Cl, Na/creatinine and Cl/creatinine ratio, 24-h urine excretion (diuresis) per 100 g of body weight, 24-h urinary Na and Cl excretion per 100 g of body weight.

Data were expressed as means \pm SD values from n animals. Using Student's t test, comparisons between the groups were made. A value of $p < 0.05$ was considered significant. Correlations between two variables were investigated by the method of linear correlation analysis. We applied the Pearson correlation coefficient r , which represents the linear relationship between two variables. A value of $p < 0.05$ was considered significant. We applied STATISTICA for Windows software (StatSoft, USA, 1995) to perform the analysis of our data.

Table 1. Diuresis and 24-h urinary sodium (Na) excretion in male and female control and VPA rat groups (mean \pm SD)

Rat groups	n	24-h diuresis (ml)	24-h Na level (mmol/l)	24-h Na excretion (mmol)	24-h Na excretion per 100 g body weight (mmol)	Na/creatinine ratio
Control females,	14	9.1 \pm 2.3	22.6 \pm 7.6	0.205 \pm 0.09	0.087 \pm 0.04*	2.90 \pm 1.62
Control males	14	8.0 \pm 2.1	19.8 \pm 13.7	0.154 \pm 0.10	0.056 \pm 0.04*	2.00 \pm 1.64
VPA females,	13	12.1 \pm 4.1*	45.1 \pm 24.7*	0.561 \pm 0.32*	0.232 \pm 0.13*	6.55 \pm 3.16*
VPA males	13	16.0 \pm 7.2*	53.9 \pm 48.4*	0.822 \pm 0.55*	0.273 \pm 0.18*	7.23 \pm 4.57*

• Statistically significant difference as compared to control group ($p < 0.05$);

* Statistically significant differences versus the other gender ($p < 0.05$).

Table 2. 24-h urinary chloride (Cl) excretion and Na/Cl ratio in male and female control and VPA rat groups (mean \pm SD)

Rat groups	n	24-h Cl level (mmol/l)	24-h Cl excretion (mmol)	24-h Cl excretion per 100 g body weight (mmol)	Cl/creatinine ratio	Na/Cl ratio
Control rats						
females	14	104 \pm 51	0.886 \pm 0.40	0.371 \pm 0.15	12.6 \pm 6.9	0.257 \pm 0.13*
males	14	168 \pm 128	1.164 \pm 0.70	0.420 \pm 0.26	14.2 \pm 8.8	0.163 \pm 0.10*
VPA rats						
females	13	180 \pm 60*	1.997 \pm 0.52*	0.833 \pm 0.22*	24.6 \pm 4.7*	0.277 \pm 0.16
males	13	275 \pm 184*	3.396 \pm 1.21*	1.208 \pm 0.53*	34.6 \pm 16.5*	0.266 \pm 0.20

• Statistically significant differences, as compared to control group ($p < 0.05$);

* Statistically significant differences versus the other gender ($p < 0.05$).

RESULTS

Diuresis, Na and Cl excretion in control rats

24-h diuresis (Table 1) in control rats showed no statistically significant gender-related differences ($p > 0.05$). 24-h diuresis per 100 g of body weight in control females (3.90 ± 1.10 ml/100 g) was significantly higher ($p < 0.02$) than in control males (2.89 ± 0.91 ml/100 g).

24-h creatinine excretion showed a tendency to be higher in control male rats (0.091 ± 0.033 mmol) versus control female rats (0.079 ± 0.034 mmol), but the difference was not statistically significant ($p > 0.05$).

24-h urine Na levels, 24-h Na excretion and the Na/creatinine ratio (Table 1) in control rats showed a tendency to be higher in female rats, but the difference was not statistically significant ($p > 0.05$). 24-h urinary Na excretion per 100 g of body weight was significantly higher in control females than in control males ($p < 0.05$).

No statistically significant gender differences in 24-h urine Cl levels, 24-h Cl excretion, 24-h Cl excretion per 100 g of body weight and Cl/creatinine ratio (Table 2) were determined in control rats ($p > 0.05$).

The Na/Cl ratio (Table 2) was significantly higher in control females than in control males ($p < 0.05$).

The 24-h urine pH showed no statistically significant difference between control females (6.57 ± 0.2) and control males (6.53 ± 0.2 ; $p > 0.05$).

The correlation between Na and Cl excretion in control males ($r = -0.08$) and control females ($r = 0.23$) was not statistically significant ($p > 0.05$). The correlation between Na excretion and 24-h urine pH in control males and females ($r = 0.11$ and $r = 0.50$) and between Cl excretion and 24-h urine pH ($r = 0.03$ and $r = 0.30$) was not statistically significant, either ($p > 0.05$).

Diuresis, Na and Cl excretion after a single dose of VPA in rats

After a single intragastric administration of 300 mg/kg sodium valproate (VPA) 24-h urine diuresis (Table 1) and 24-h diuresis per 100 g of body weight (5.04 ± 1.66 ml/100g in VPA-females and 5.38 ± 2.41 ml/100g in VPA-males) were significantly ($p < 0.05$) higher in both genders (without statistically significant gender-related differences).

24-h urine Na levels, 24-h Na excretion, 24-h urinary Na excretion per 100 g of body weight and Na/creatinine ratio (Table 1) were significantly higher ($p < 0.02$) in male and female rats. There were no gender-related differences in diuresis and Na excretion after administration of VPA.

24-h urine Cl levels (Table 2) were significantly ($p < 0.05$) higher in both genders of experimental

animals. 24-h urinary Cl excretion, 24-h urinary Cl excretion per 100 g of body weight and the Cl/creatinine ratio (Table 2) in both sexes of VPA rats were significantly higher than in gender-matched controls ($p < 0.001$). Chloride excretion (24-h urinary Cl excretion, 24-h urinary Cl excretion per 100 g of body weight and the Cl/creatinine ratio) was found significantly higher in VPA-male than in VPA-female rats ($p < 0.05$). 24-h creatinine excretion in VPA-male rats (0.110 ± 0.025 mmol) was significantly higher than in VPA-female rats (0.082 ± 0.017 mmol; $p < 0.005$).

The Na/Cl ratio (Table 2) in VPA-rats did not show statistically significant difference as compared to controls and between the genders ($p > 0.05$).

The 24-h urine pH in VPA males (6.42 ± 0.3) and VPA females (6.43 ± 0.3) showed no statistically significant differences versus controls and between the genders ($p > 0.05$).

A correlation between Na and Cl excretion was not statistically significant in VPA-female ($r = 0.54$; $p > 0.05$) and VPA male rats ($r = 0.06$; $p > 0.05$). The correlation between Na excretion and 24-h urine pH was not statistically significant ($p > 0.05$) in VPA female ($r = 0.21$) and VPA male rats ($r = 0.14$). The correlation between Cl excretion and 24-h urine pH was significant only in VPA males ($r = -0.72$; $p < 0.05$). The correlation between Cl excretion and 24-h urine pH in VPA females ($r = 0.02$) was not significant ($p > 0.05$).

DISCUSSION

There are increasing evidences indicating that certain drugs evoke adverse effects that depend on the gender of patients. Therefore, elucidation of gender-effect of various drugs by means of preclinical investigation is an important field of pharmacology.

Study data show that after a single intragastric administration of 300 mg/kg VPA 24-h urine diuresis and 24-h diuresis per 100 g of body weight were significantly higher in VPA rats of both genders. Other investigators showed VPA administration to be related to a significant increase in the volume of urine in rats (8). Diuresis is directly related to Na excretion (9).

24-h diuresis per 100 g of body weight in control female rats was found significantly higher than in control male rats. 24-h urinary Na excretion per 100 g of body weight was significantly higher in control female rats than in control male rats. Otherwise, the Na/Cl ratio was significantly higher in control female rats than in control male rats. Basal fractional excretion of Na was significantly lower in male as compared to female rats at a similar lower renal perfusion pressure (10). The determined gender-related difference of Na excretion could be dependent of gender-related differences of Na and Cl metabo-

lism in rats. Female rats drank more of 3% NaCl solution than did males. Female rats consistently ingested about twice as much NaCl solution as did male rats, regardless of the palatability of the solution or of body Na levels (11). On the other hand, Na appetite elicited by a prolonged Na deprivation is higher in male than in female rats (12). Exogenous testosterone lowered Na intake in adult rats of both sexes (13). Female rats have a lower renal hemodynamics as compared to male (14–16).

The observed gender-dependent differences could be related with gender-specific Na and Cl ion transport and homeostasis peculiarities in rats. The renal excretion of Na and Cl is, in part, controlled by gender differences in the renal density of the thiazide diuretic receptors (17). The density of the thiazide receptor was twofold higher in female than in male rats (17, 18).

The present study shows the influence of VPA on Na and Cl excretion in Wistar rats. After a single administration of VPA, 24-h urine Na levels, 24-h urine Na excretion, 24-h urinary Na excretion per 100 g of body weight and Na/creatinine ratio were significantly higher in male and female rats than in gender-matched controls. 24-h urinary Cl excretion, 24-h urinary Cl excretion per 100 g of body weight and Cl/creatinine ratio were significantly higher in VPA-male than in VPA-female rats. These data show that VPA might exert a gender-related effect on Na and Cl excretion in urine.

Na and Cl channels play a critical role in the functioning of the nervous system by asserting control over the voltage potentials across the plasma membrane (4).

One of the causes of hyponatremia, the syndrome of inappropriate antidiuretic hormone secretion, has been associated with some antiepileptic drugs, including VPA (1, 2, 19). The mechanisms by which antiepileptic medicines decrease serum Na levels may be similar, but the pathomechanism of hyponatremia is not yet clear. An increased sensitivity of Na transport systems in the renal tubules to the circulating vasopressin cannot be excluded. It has been suggested that antiepileptic medicines cause an increase in AVP secretion or have a direct tubular effect in the kidney, but the data are conflicting (20–22). The classical short-term effect (within minutes) of vasopressin consists in increasing Na, Cl and water transport in kidney cells. More recently, long-term actions (several hours) of vasopressin have been evidenced on water and Na fluxes, due to transcriptional enhancement in the expression of Na/K/2Cl co-transporter (23). Vasopressin is also responsible for a long-term increase in net chloride secretion (23). The increase in renal Na excretion in response to physiological doses of arginine vasopressin is not directly linked to the V2-mediated antidiuretic effect. The V1 receptor mediates the natriuretic effect of vasopressin

in rats (24). The experimental *in vivo* results provide evidence that tubular V1 vasopressin receptor activity results in increased urine flow in the euvoletic state in rats (25). Increased Na excretion in male rats could be related with activated hemodynamics as well, because the pressor response to vasopressin secretion is greater in males vs. females due to a reduced total peripheral resistance in female rats (26).

The GABAA is an ionotropic receptor whose subunits form a functional Cl channel (6, 7). The Cl channel of the GABAA receptor is activated by VPA (5). It has been shown that GABAA receptor subunits are expressed in the Wistar rat kidney proximal convoluted and straight tubules (27).

Our data show a positive correlation between Cl excretion and 24-h urine pH, which was significant only in VPA-males. The alkaline extracellular pH increases the GABAA channel opening frequency and decreases the duration of the long closed state in rat hypothalamus (28). The physiological function of GABAA in the kidney is not known. However, our findings allow to hypothesize that GABAA subunits play a role in basolateral membrane Cl transport. These findings offer a possibility that other subunits of the ligand-gated Cl channel superfamily could be involved in renal Cl excretion (27).

Elucidation of VPA-induced mechanisms of obviously enhanced Cl excretion could be of value while explaining the pharmacological basis of VPA action in renal tissue. Male gender increases sensitivity to renal injury in response to some factors (39). There are investigational data that VPA could induce dysfunction of proximal renal tubules (30), in which about 40 percent of Cl is reabsorbed (31). Chloride channel openers are said to be nephrotoxic. Literature data show that epilepsy treatment with VPA in children could be related to its nephrotoxic effect (30, 32, 33). Thus, further studies of the mechanisms of VPA natriuretic and chloriuretic effect could be important.

CONCLUSIONS

VPA, alongside the diuretic effect, enhances Na and Cl excretion with urine in both genders of rats. The 24-h natriuretic and chloriuretic response to VPA in male rats was significantly higher than in female rats. The mechanism of such gender-related effect is not clear. The above reported experimental observations may have potentially important pharmacological implications.

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ŪMUS VALPROATŲ POVEIKIS PIURKIŲ NATRIO IR CHLORIDO IŠSISKYRIMUI SU ŪLAPIMU

S a n t r a u k a

Daugėja duomenų apie su lytimi susijusias nepageidaujamas reakcijas š vaistą, kurių išaiškinimas yra svarbi šiandieninės farmakologijos sritis. Yra duomenų apie valproatų sukeltą hiponatremiją, kuri yra dažnesnė ir sunkesnė moterims. Mūsų darbo tikslas buvo nustatyti Wistar piurkių natrio (Na) ir chlorido (Cl) išsiskyrimo su paros ūlapimu ypatumus bei natrio valproato (VPA) poveiką šiai ekskrecijai. Matavo-

me Na, Cl, kreatinino koncentracijas paros ūlapime ir ūlapimo pH. Ištyrėme 28 kontrolines Wistar piurkes (14 patinėlių ir 14 patelių) ir 26 Wistar piurkes (13 patinėlių ir 13 patelių) po vienkartinės 300 mg/kg VPA dozės, suleistos š skrandą

Nustatėme, kad kontrolinių piurkių patelių paros diurezė, Na išsiskyrimas (100 g kūno svorio) ir Na/Cl santykis yra patikimai didesni negu patinėlių. Mūsų tyrimai rodo, kad natrio valproatas patikimai padidina diurezę, Na ir Cl išsiskyrimą su ūlapimu abiejų lyčių piurkėms ir kad šis poveikis patinėliams yra patikimai ryškesnis, tačiau jo mechanizmai šiandien nėra aiškūs.

Raktaodžiai: valproatai, natrio, chloridas, ūlapimas, piurkės, lytis