Gender differences of sodium metabolism and hyponatremia as an adverse drug effect

Jurgita Grikinienė, Voldemaras Volbekas[1], Donatas Stakišaitis[2]
Vilnius University Children Hospital, [1]Department of Basic and Clinical Pharmacology, Kaunas University of Medicine, [2]Institute of Oncology, Vilnius University, Lithuania

Key words: *hyponatremia, sodium, gender differences, adverse drug effect.*

Summary. *Gender-related differences in sodium (Na^+) metabolism, Na^+ transport through cell membrane, intracellular Na^+ concentration, and Na^+ urinary excretion review is presented in the article. Literature data on gender-related differences in the occurrence of hyponatremia and related neurology are overviewed. Some of the drugs used in neurology (carbamazepine, oxcarbazepine, thiazides, antidepressants) are pointed out as eventual sources of hyponatremia. This disorder shows a clear-cut preference of the feminine gender. The authors present literature data on gender-related differences in the mechanisms of Na^+ transport (Na^+/H^+ exchange, $Na^+/K^+/2Cl^-$ cotransport, Na^+, K^+-ATPase). The reasons for such differences are not yet known. Investigative tests with animals of both genders, cellular studies and clinical investigations with human males and females could help to answer question why females are more prone to hyponatremia, to select more efficient measures for prevention of hyponatremia and to differentiate specific peculiarities of treatment for patients of either sex.*

Introduction

There are accumulative data indicating that sodium (Na^+) metabolism, Na^+ transport across the cell membrane, and intracellular sodium ($[Na^+]_i$) concentration depends on gender. Clinical and experimental observations suggest a possible difference in response to dietary sodium chloride (salt sensitivity) in females compared to males due to the intermediate effects of the sex hormone pattern and gender-related genetic factors (1, 2). We should note here the well-known high frequency of acute symptomatic hyponatremia and increased death rate in women as well as in female animals of childbearing age (3, 4), which also shows a gender-dependent difference in Na^+ metabolism. So far there have been no exhaustive studies concerning determination of gender-related differences of Na^+ transport mechanisms in the cell. For instance, the absolute majority of Na^+ transport studies have been developed on the grounds of assays performed in male cell cultures or male experimental animals. There are evidences indicating that certain drugs could be the reason of hyponatremia as an adverse drug effect, which also depends on gender of patients. There are almost no studies on pre-marketing evaluation of drug effects in women, which is sometimes explained by ethical reasons. Theoretically women are rather unmotivated in the face of certain medicines, and this situation becomes even more serious in the light of new data indicating that women more frequently than men suffer from pathological changes of Na^+ metabolism. So the next important academic step is to broaden the way of the evaluation of gender-related differences in adverse drug reactions. The present paper is intended as a contribution to this purpose.

Hyponatremia, age and gender. Despite several decades of research, many aspects of hyponatremic disorders remain unclear. Death or brain damage associated with hyponatremia has been described since 1935. Common clinical examples of hyponatremia include hastened rehydration therapy, dialysis disequilibrium syndrome, compulsive polydipsia and others. Hyponatremia can be caused by several conditions, such as malignancies, non-malignant pulmonary diseases, intracranial infections, traumas and other disorders of central nervous system, hypoadrenalism, hypothyroidism after surgery and as a side effect of numerous drugs (5). Patients with hyponatremia are exposed to major neurological complications. Hyponatremia causes passive water influx and swelling of brain cells and produces brain edema, promotes hyperexcitability and epileptiform activity (5–7).

Hyponatremia was the cause of seizures in 70% of infants younger than 6 months of age, suffering from seizures; median seizure duration was longer in

Correspondence to J. Grikinienė, Vilnius University Children Hospital, Santariškių 7, 08406 Vilnius, Lithuania
E-mail: jurgita.grikiniene@mf.vu.lt

hyponatremic patients with greater incidence of *status epilepticus* compared with normonatremics (8). The lower serum Na^+ level, the higher is the probability of a repeated convulsion (9, 10).

Children and menstrual women are most susceptible to brain damage from hyponatremia (6, 7). The relative risk of death or permanent brain damage from hyponatremic encephalopathy was 28 times higher in women as compared to men and 26 times higher in menstrual women if compared with postmenopausal women (11). Menstrual women also are most susceptible to experience brain demyelination so called *central pontine myelinolysis* or *osmotic demyelination syndrome* caused by an excessive correction of hyponatremia (12). Exercise-associated hyponatremia in marathon runners also is more common in women than in men (13). So factors that are suspected to aggravate the prognosis of hyponatremic encephalopathy are feminine gender (menstrual women) and young age.

With chronic hyponatremia, the mortality was 13% in adult male rats *versus* 62% in female rats. With acute hyponatremia, the mortality reached 84% in prepubertal rats *versus* 15% in adult and 9% in elderly rats. Testosterone pretreatment significantly decreased the mortality from 62% to 9% in adult female rats, and from 100% to zero in prepubertal rats, but estrogen significantly increased it from 13% to 44% in adult male rats. Thus, age and gender are the major determinants of mortality in experimental hyponatremic encephalopathy (14–16).

Hyponatremia as an adverse drug effect. Hyponatremia has been associated with several drugs, such as antiepileptic drugs: carbamazepine (17–20), oxcarbazepine (17, 21–26) valproate (27, 28), lamotrigine (29); psychotropic drugs: neuroleptics, tricyclic antidepressants, selective serotonin reuptake inhibiting antidepressants (30–34); diuretics (35, 36); desmopressin (37, 38); lisinopril (39), MDMA (ecstasy) (40) and others.

Carbamazepine (CBZ) has led to hyponatremia in neurological patients with a frequency varying from 4.8% to 40% (17), female gender may have played a role in the development of hyponatremia (18, 19). The risk of hyponatremia increases with age (subjects older than 30 years had four times higher prevalence of hyponatremia than those younger than 30 years) and is more frequent in elderly patients (20).

Hyponatremia (albeit often asymptomatic and benign) may be more common during treatment with oxcarbazepine than with carbamazepine in adults and children (17, 21). The frequency varies from 2.7% to 41% and more (22, 23, 25, 26), most frequently in patients with diseases or medications predisposing to hyponatremia, especially in elderly patients (26).

According to the data of the World Health Organization (WHO) International Drug Monitoring Center, 78% of antidepressant-associated hyponatremia disorders concerns women (30). Hyponatremia may be relatively common early asymptomatic side effect of serotonin re-uptake inhibitors, especially in older women (28% of the patients on fluoxetine and 22% on paroxetine) (31). Potential risk factors for hyponatremia due to psychotropic medications included advanced age, female gender, and use of concomitant medications, which are known to cause hyponatremia (33, 34).

Thiazides-induced hyponatremia is four times more common in women than in men (35). The only risk factor for hyponatremia after MDMA ingestion is female gender (40).

Hyponatremia occurred in 24% of patients with multiple sclerosis treated with desmopressin and it appeared to be dose-dependent (37). It is well known that women have a higher prevalence of multiple sclerosis. The frequency of hyponatremia in women after treatment with antidepressants also could be related to gender differences in the frequency of depression, because the prevalence of depressive disorders in women is higher than in men. So data on hyponatremia developing after treatment of the mentioned diseases in women become more important for establishing such a relationship.

Link between hyponatremia and inappropriate secretion of vasopressin. The mechanisms of hyponatremia related with certain medicine have been postulated to be associated with the syndrome of inappropriate secretion of the antidiuretic hormone (SIADH). Normally, antidiuretic hormone is secreted when effective circulating blood volume is decreased. SIADH is marked by increased secretion of antidiuretic hormone in the presence of normal circulating blood volume. That causes plasma hyponatremia simultaneously with plasma hypoosmolality and inappropriate hyperosmolality of the urine. SIADH with hyponatremia has been associated with some drugs, including carbamazepine (17), sodium valproate (27, 28), lamotrigine (29), selective serotonin reuptake inhibitors (32, 33) and was found to be more frequent in women. Thiazides- (35) and amiloride-induced hyponatremia (36, 41) was found to be related with an excess vasopressin activity as well.

Studies show that plasma arginine vasopressin is involved in the mechanisms causing hyponatremia and vasopressin concentration is increased in most children and adults with hyponatremia (42, 43). It has been

reported repeatedly that synthetic vasopressin (desmopressin) shows a serious potential for hyponatremia and seizures (37, 38). Non-osmotic stimulation of arginine vasopressin release and lack of suppression of this hormone is an important pathogenetic mechanism of hyponatremia in children due to altered sensitivity to serum osmolality by the hypothalamic osmoreceptors, dysregulation in hypothalamic centers, manifesting in hypersecretion of arginine vasopressin and osmodysregulation (42).

Association of hyponatremia and increased concentration of serum antidiuretic hormone strongly suggest the presence of SIADH, though some authors find oxcarbazepine- and carbamazepine -induced hyponatremia without a concomitant increase in the arginine vasopressin serum levels. These findings indicate that in these cases hyponatremia is not attributable to the SIADH and possible mechanisms include a direct effect of drugs on the renal collecting tubules or an enhancement of their responsiveness to circulating antidiuretic hormone (17, 24).

Gender-related differences in responsiveness to arginine vasopressin. There is a gender-related difference in the antidiuretic responsiveness to endogenous arginine vasopressin (AVP). This difference is dependent upon the ovarian hormones. Gonadectomy had no effect on the antidiuretic potency of vasopressin in male rats, but gonadectomy decreased urine flow and increased urine osmolarity in female rats (44). Intravenous infusion of hypertonic saline resulted in a greater increase in the urinary excretion of AVP in women than in men. This would appear to suggest a greater osmotic sensitivity of AVP release in women than in men (45).

The basal plasma AVP levels, as well as the 24-hour urinary excretion of AVP, are higher in men than in women (46). This would indirectly support the idea about a higher sensitivity of AVP in females as well.

The higher mortality in hyponatremic female rats treated with AVP was associated with a decrease in cerebral perfusion compared with either normonatremic females or males. Because male rats with a similar degree of chronic AVP-induced hyponatremia had a low mortality and no decrease in cerebral perfusion, the data suggested that the deterioration of cerebral perfusion might be a cause of the increased mortality from AVP-induced hyponatremia in female rats. The decrease of cerebral perfusion in hyponatremic female rats appears to be a consequence of the combined cerebrovascular effects of some aspects of female gender plus AVP, plus hyponatremia, because it is absent in male rats (47). After induction of hyponatremia in prepubescent rats for over four hours with water and vasopressin, an 18% decrease in plasma Na^+ was associated with a 13% increase in brain water and a decrease in brain sodium (48). Additionally, after administration of vasopressin there were found a decreased high-energy phosphate generation, an elevated inorganic phosphate level, and intracellular acidosis in brain cells of only female rats (16).

The increased mortality observed in female rats with AVP-induced hyponatremia appears to be related in part with the combined effects of AVP acting on cerebral blood vessels via AVP V_1 receptors (47). It has been shown that AVP-induced brain edema is mediated by the AVP V_1 receptor (49).

AVP through stimulation of V_1 receptors may cause constriction and spasm of cerebral blood vessels (50) and reduce cerebral blood flow (51). The sensitivity of isolated rat aortic rings to AVP was greater in rings obtained from female than from male (52). Our data showed that chloride transport sensitivity to AVP in vascular smooth muscle cells of female was higher than of male rats (53).

The brain damage associated with hyponatremia in adults requires the presence of AVP, and it is attenuated by male gender and is accelerated by female gender or estrogen pre-treatment (47). Treatment with estradiol increased the density of AVP binding sites in membranes prepared from the mesenteric bed, leading to an increase in the pressure response to AVP (54).

It has been established that cAMP is a second messenger for AVP action. AVP enhancement of agonist-stimulated cAMP accumulation in vascular smooth muscle cells is mediated by V_1 receptors, because the effect of AVP was completely inhibited by the V_1-receptor antagonists (55). Findings indicate that central cholinergic and angiotensinergic mechanisms controlling AVP release are influenced differently by gender also (56).

The mentioned evidences corroborate the hypothesis that in most of female patients hyponatremia could be caused by SIADH and increased sensitivity of antidiuretic hormone. Altered sensitivity of the hypothalamic receptors to serum AVP and increased sensitivity of the renal tubules to circulating AVP can appear as well. Specific blocking drugs of AVP receptors could make a significant contribution to the understanding of gender-related difference of AVP effects, as well as to elucidation of hyponatremia mechanisms and management of sodium homeostasis (57).

Total body and blood serum sodium, salt intake, salt sensitivity and gender. Total body Na^+ remained constant throughout the age span studied in healthy males, but decreased slightly in females over 60 years

of age. Na^+ excess defined as the amount of body sodium in excess of body chloride was found to be correlated with total body calcium (58). Total body Na^+ was correlated with total body chloride and total body calcium (59).

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 sodium levels (60). On the other hand, sodium appetite elicited by prolonged sodium deprivation is higher in males compared with females (61). Male rats castrated at 1st day of age drank 3% NaCl in adulthood in a manner similar to females. Castration in adulthood of male and female rats did not change their Na^+ consumption. Exogenous testosterone lowered Na^+ intake in adult rats of both sexes (62).

The intake of Na^+ depends on physical activity in women: more active young women showed lower absolute intakes of sodium in comparison with less active young women (63). Women ultradistance triathletes had significantly lower plasma sodium concentrations than men (64). Evidences of hyponatremia are accompanied by elevated urine sodium concentration and excessive urine output (65).

Only in men aged-adjusted systolic and diastolic blood pressure correlated significantly with dietary Na^+ intake, suggesting an increasing sensitivity to dietary sodium with age in men (1). Women who had significantly lower body weight tended to be more often than men salt-sensitive with ageing (2).

Na^+ excretion in urine and gender. Women had significantly lower ratios of 24-hour to overnight excretion of sodium than men did (66). Only among white healthy students a significant sex-related difference was observed in urinary Na^+ excretion rates, whereas males excreted higher rates than females (67). Females excreted Na^+ by about 20–25% less than did males (68).

The 24-hour urinary Na^+ excretion showed a significant correlation with systolic and diastolic blood pressure in 50–54 year old men, but not in women of the same age (69). Higher urinary sodium is also associated with substantially greater differences in blood pressure in middle age compared with young adulthood (70).

Analysis showed a significant inverse relationship between daily Na^+ excretion and systolic blood pressure, as well as between daily Na^+ excretion and diastolic blood pressure among premenopausal women. Such relationship disappeared after menopause. This fact could be a confirmation of the association between Na^+ excretion and blood pressure in premenopausal women and menstruation as a protective action against the hypertensive effect of sodium (71).

The association between urinary Na^+ excretion and blood pressure tended to be more marked in older as compared to younger ages and in women compared with men (69–72).

A reduction in salt consumption significantly decreased (by 25 mmol/24 h) the 24-hour urinary excretion of sodium in young women compared with control group, and in adult men the changes were not different compared with control group (73).

For a given Na^+ excretion, elderly men excrete more calcium than women: there was a clear-cut correlation between urinary sodium and calcium both in men and women, but the regression coefficient was significantly higher in men than in women (74).

Intracellular Na^+ and gender. Intracellular concentrations of Na^+ have been shown to be different in men than in women. Healthy females showed a significantly lower mean value of various type cellular $[Na^+]_i$ content as compared to males (75, 76). In healthy volunteers, erythrocyte (red blood cell) Na^+ levels increased with increase in age, body weight and mean arterial pressure in both sexes (77, 78).

In healthy women the Na^+ concentrations in red blood cell are lower during the luteal phase of the menstrual cycle than in the follicular phase and than in men (79, 80).

Gender-related differences in $[Na]_i$ concentration most likely result from gender-related differences in the function of Na^+ transport systems (Na^+/H^+ exchanger, $Na^+/K^+/2Cl^-$ cotransport, Na^+, K^+-pump).

Na^+/H^+ antiport and gender. This system is involved in the regulation of intracellular pH ($[pH]_i$). G. Tokudome et al showed gender variations in the pH_i set point of activation of the Na^+/H^+ antiport: men demonstrated an alkaline shift in the pH_i set point for activation of the Na^+/H^+ antiport compared with women in lymphocytes (81).

Na^+/H^+ exchange in mice renal brush-border membranes exhibit strong sex differences, i. e., this rates in males being higher than in females. Castration of male mice led to a decrease in Na^+/H^+ exchange to values found in females. Treatment of castrated mice with estradiol had no effect. In contrast, treatment with testosterone increased the rate of the exchanger by more than 100% (82).

$Na^+/K^+/2Cl^-$ cotransport and gender. This system cotransport Na^+ and K^+ and it is electrically neutral, because it also transports Cl^-. The mean value of $Na^+/K^+/2Cl^-$ cotransport in RBC was by 26–46% higher in men than in women (75, 83). Cotransport activity is lower in women during the follicular phase

than in men (79). $Na^+/K^+/2Cl^-$ cotransport was found to be the lowest in ovulatory women and the highest in men (84). In contrast, other authors showed that $Na^+/K^+/2Cl^-$ cotransport is unchanged during the menstrual cycle in female (85).

Na^+, K^+-adenosinetriphosphatase pump (Na^+, K^+-ATPase) and gender. Chinese women had more Na^+, K^+-pumps in lymphocytes than Chinese men, but Indian subjects did not show this pattern (76).

Significant sexual differences in RBC were noted for ouabain-sensitive and ouabain-insensitive Na^+ efflux, for intracellular sodium concentration and with higher values for men than for women. Among all subjects, significant correlation was found between $[Na]_i$ concentration and the number of Na^+, K^+-ATPase sites per erythrocyte and between the ouabain-sensitive sodium efflux per site and $[Na]_i$ (75). Data from several studies indicate that Na^+, K^+-ATPase pump function in female heart, ileum, liver, brain tissues is markedly less than in males. It was suggested that the Na^+, K^+-adenosinetriphosphate pump function in female rat brain synaptosomes is less effective than in male as well (86). Moreover, it has been shown that female sex hormones (estrogen and progesterone) can inhibit Na^+, K^+-ATPase enzyme activity in many tissues, whereas the male sex hormone (testosterone) may stimulate enzyme activity (86–88). These mechanisms could appear responsible for increased awareness of acute symptomatic hyponatremia and increased death rate in women as well as female animals of childbearing age (3, 4).

Na^+, K^+-ATPase activity, as determined by ouabain-sensitive ^{86}Rb influx, was the same in men and ovulatory women groups, but it was significantly suppressed in women taking combined oral contraceptive preparations compared with both men and ovulatory women. These differences were not due to alterations in either progesterone or aldosterone, but could represent an androgenic effect *in vivo* of the testosterone derivatives in combined oral contraceptive preparation (89).

Conclusion

The data under review indicate that cellular Na^+ homeostasis may differ in males and females. Hyponatremia, usually without clinical significance, may sometimes lead to serious complications when overlooked or not properly treated. The reasons for the increased female susceptibility to complications from hyponatremia are, however, unclear. Gender-specific relationship between hyponatremia and Na^+ transport mechanisms will need to be included in the studies of animal and cell models as they appear to help in better identification of specific genetic-environmental/medicines association and interactions. Adverse drug effects analysis in relation with gender provides important additional information, which supports the urgency of investigation of gender-related peculiarities of Na^+ metabolism and differences in Na^+ transport mechanisms. The pathophysiological mechanisms that result in hyponatremia must be explored so that this occurrence and its consequences could be prevented.

Su lytimi susiję natrio apykaitos skirtumai, vaistų sukelta hiponatremija

Jurgita Grikinienė, Voldemaras Volbekas[1], Donatas Stakišaitis[2]

Vilniaus universiteto vaikų ligoninė, [1]Kauno medicinos universiteto Teorinės ir klinikinės farmakologijos katedra, [2]Vilniaus universiteto Onkologijos institutas

Raktažodžiai: hiponatremija, natris, lyties skirtumai, nepageidaujamas vaistų poveikis.

Santrauka. Straipsnyje pateikiami literatūros duomenys apie su lytimi susijusius natrio (Na^+) metabolizmo, Na^+ pernašos per ląstelės membraną ((Na^+/H^+ pasikeitimo, $Na^+/K^+/2Cl^-$ pernašos, Na^+, K^+-ATFazės), intraląstelinio Na^+ koncentracijos ir Na^+ pasišalinimo su šlapimu skirtumus. Medicinos literatūroje aprašyti su lytimi susiję hiponatremijos ir dėl jos atsiradusios neurologinės patologijos skirtumai. Kai kurie vaistai, vartojami nervų ligoms gydyti (karbamazepinas, okskarbazepinas, tiazidai, antidepresantai ir kiti), gali sukelti hiponatremiją, kuri dažnesnė moterims. Šių skirtumų kilmė kol kas neaiški. Eksperimentiniai tyrimai su abiejų lyčių gyvūnais, ląstelių metabolizmo tyrimai, abiejų lyčių klinikinės studijos gali padėti atsakyti į klausimą, kodėl moterims dažniau išsivysto hiponatremija, ir rasti efektyvius hiponatremijos profilaktikos bei gydymo metodus.

Adresas susirašinėti: J. Grikinienė, Vilniaus universiteto vaikų ligoninė, Santariškių 7, 08406 Vilnius
El. paštas: jurgita.grikiniene@mf.vu.lt

References

1. Yagil Ch, Sapojnikov M, Kreutz R, Katni G, Lindpaintner K, Ganten D, et al. Salt susceptibility maps to chromosomes 1 and 17 with sex specificity in the Sabra rat model of hypertension. Hypertension 1998;31:119-24.
2. Kojima Sh, Murakami K, Kimura G, Sanai T, Yashida K, Imanishi M., et al. A gender difference in the association between salt sensitivity and family history of hypertension. Am J Hypertens 1992;5:1-7.
3. Ayus JC, Krothapalli RK, Arieff I. Sexual difference in survival with severe symptomatic hyponatremia (abstract). Kidney Int 1988;33:181.
4. Fraser CL, Kucharczyk J, Arieff AI, Rollin C, Spernacki P, Norman D. Sex difference result in increased morbidity from hyponatremia in female rats. Am J Physiol 1989;256:R880-5.
5. Palmer BF. Hyponatremia in patients with central nervous system diseases: SIADH versus CSW. Trends Endocrinol Metab 2003;14:182-7.
6. Fraser CL, Arief AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med 1997;102:67-77.
7. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. Clin Nephrol 1996;46:149-69.
8. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ. Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med 1995;26:42-8.
9. Hugen CA, Oudesluys-Murphy AM, Hop WC. Serum sodium levels and probability of recurrent febrile convulsions. Eur J Pediatr 1995;154:403-5.
10. Kiviranta T, Airaksinen EM. Low sodium levels in serum are associated with subsequent febrile seizures. Acta Paediatr 1995;84:1372-4.
11. Ayus JC, Wheeler JM, Arief AI. Postoperative hyponatremic encephalopathy in menstrual women. Ann Intern Med 1992;117:891-7.
12. Decaux G, Soupart A. Hypotonic hyponatremia: therapeutic and controversial aspects. Nephrologie 1994;15:21-6.
13. Almond CS, Fortescue EB, Shin AY, Mannix R, Greenes DS. Risk factors of hyponatremia among runners in Boston marathon. Acad Emerg Med 2003;10:534-5.
14. Arief AI, Kozniewska E, Roberts TP, Vexler ZS, Ayus JC, Kucharczyk J. Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 1995;268:R1143-52.
15. Kozniewska E, Roberts TP, Vexler ZS, Oseka M, Kucharezyk J, Ariel AI. Hormonal dependence of the effects of metabolic encephalopathy on cerebral perfusion and oxygen utilization in the rat. Circ Res 1995;76:551-8.
16. Uchida K, Takahashi N, Sumikura T, et al. Evaluation of the changes in intracranial water, sodium, phosphorus metabolites and intracellular pH in rats with acute dilutional hyponatremia. Nippon Jinzo Gakkai Shi 1990;32:1169-77.
17. Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia 1994;35:181-8.
18. Brewenton TD, Jackson CW. Prophylaxis of carbamezepine-induced hyponatremia by demeclocycline in six patients. J Clin Psychiatry 1994;55:249-51.
19. Inamura T, Kuba H, Morioka T, Muratani H, Muraishi M, Hisada K, et al. Carbamazepine induced hyponatremia. No Shinkei Geka 1999;27:85-7.
20. Leppik IE. Metabolism of antiepileptic medication: newbobn to elderly. Epilepsia 1992;4:S32-40.
21. Borusiak P, Korn-Merker E, Holert N, Boenigk HE. Hyponatremia induced by oxcarbazepine in children. Epilepsy Res 1998;30:241-6.
22. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine-induced hyponatremia, a cross-sectional study. Epilepsy Res 1988;2:269-71.
23. Holtmann M, Krause M, Opp J, Tokarzewski M, Korn-Merker E, Boenigk HE. Oxcarbazepine-induced hyponatremia and the regulation of serum sodium after replacing carbamazepine with oxcarbazepine in children. Neuropediatrics 2002;33:298-300.
24. Sachdeo RC, Wasserstein A, Mesenbrink PJ, D'Souza J. Effects of oxcarbazepine on sodium concentration and water handling. Ann Neurol 2002;51:613-20.
25. Wellington K, Goa KL. Oxcarbazepine: an update of its efficacy in the management of epilepsy. CNS Drugs 2001;15:137-63.
26. Kutluay E, McCague K, D'Souza J, Beydoun A. Safety and tolerability of oxcarbazepine in elderly patients with epilepsy. Epilepsy Behav 2003;4:175-80.
27. Branten AJ, Wetzels JF, Weber AM, Koene RA. Hyponatremia due to sodium valproate. Ann Neurol 1998;43:265-7.
28. Miyaoka T, Seno H, Itoga M, Kishi T, Ishino H, Horiguchi J. Contribution of sodium valproate to the syndrome of inappropriate secretion of antidiuretic hormone. Int Clin Psychopharmacol 2001;16:59-61.
29. Mewasingh L, Aylett S, Kirkham F, Stanhope R. Hyponatremia associated with lamotrigine in cranial diabetes insipidus. Lancet 2000;356:656.
30. Spigset O, Hedenmalm K. Hyponatremia in relation to treatment with antidepressants: a survey of reports in the World Health Organization Data base for spontaneous reporting of adverse drug reactions. Pharmacotherapy 1997;17:348-52.
31. Strachan J, Shepherd J. Hyponatremia associated with the use of selective serotonin re-uptake inhibitors. Aust N Z J Psychiatry 1998;32:295-8.
32. Romerio SC, Radanowicz V, Schlienger RG. SIADH with epileptic seizures and coma in fluoxetine therapy. Schweiz Rundsch Med Prax 2000;89:404-10.
33. Barclay TS, Lee AJ. Citalopram-associated SIADH. Ann Pharmacother 2002;36:1558-63.
34. Madhusoodanan S, Bogunovic OJ, Moise D, Brenner R, Markowitz S, Sotelo J. Hyponatremia associated with psychotropic medications. A review of literature and spontaneous reports. Adverse Drug React Toxicol Rev 2002;21:17-29.
35. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. [Review]. Chest 1993;103:601-6.
36. van Assen S, Mudde AH. Severe hyponatremia in an amiloride/hydrochlorothiazide-treated patients. Neth J Med 1999;54:108-13.
37. Valiquette G, Herbert J, Maede-D'Alisera P. Desmopressin in the management of nocturia in patients with multiple sclerosis. A double-blind, crossover trial. Arch Neurol 1996;53:1270-5.
38. Bernstein SA, Williford SL. Intranasal desmopressin-associated hyponatremia: a case report!and literature review. J Fam Pract 1997;44:203-8.
39. Subramanian D, Ayus JC. Case report: severe symptomatic

hyponatremia associated with lisinopril therapy. Am J Med Sci 1992;303:177-9.
40. Balmelli C, Kupferschmidt H, Rentsch K, Schneemann M. Fatal brain edema after ingestion of ecstasy and benzylpiperazine. Ditsh Med Wochenschr 2001;126:809-11.
41. Coscoy S, de Weille J, Lingueglia E, Fukuda N, Matthay M, Lazdunski M, et al. Amiloride-sensitive sodium channel in the nephron and its activation by vasopressin. Ann Endocrinol (Paris) 2000;61:145-6.
42. Gerigk M, Bald M, Feth F, Rascher W. Clinical settings and vasopressin function in hyponatremic children. Eur J Pediatr 1993;152:301-5.
43. Ishikawa S, Fujita N, Fujisava G, Tsuboi Y, Sakuma N, Okada K, et al. Involvement of arginine vasopressin and renal sodium handling in pathogenesis of hyponatremia in elderly patients. Endocr J 1996;43:101-8.
44. Wang YX, Crofton JT, Miller J, Sigman CJ, Liu H, Humber DP, et al. Sex difference in urinary concentration ability of rats with water deprivation. Am J Physiol 1996;270:R550-55.
45. Merkelbach U, Czernichow P, Gaillard RC, Vallotton MB. Radioimmunoassay of [8-arginine]-vasopressin. II. Application to determination of antidiuretic hormone in urine. Acta Endocrinol 1975;80:453-64.
46. Crofton JT, Baer PG, Share L, Brooks DP. Vasopressin secretion in normotensive black and white men and women on normal and low sodium diets. J Endocrinol 1986;108:191-9.
47. Arieff AI, Kozniewska E, Roberts TPL, Vexler ZS, Ayus JC, Kucharczyk J. Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 1995;268:R1143-52.
48. Silver SM, Schroeder BM, Bernstein P, Sterns RH. Brain adaptation to acute hyponatremia in young rats. Am J Physiol 1999;276:R1595-9.
49. Rosenberg GA, Estrada E, Kyner WT. Vasopressin-induced brain edema is mediated by the V1 receptor. Adv Neurol 1990; 52:149-54.
50. Gardiner SM, Compton AM, Bennett T. The effects of infusions of arginine vasopressin or 1-deamino-8-D-arginine vasopressin on common carotid vascular resistance in conscious Long Evans rats. Br J Pharmacol 1989;97:153-7.
51. Kozniewska E, Oseka M, Stys T, Melin P, Trojnar J. Does nitric oxide contribute to the effect of a vasoconstricting analog of vasopressin on cerebral blood flow? J Cereb Blood Flow Metab 1993;13 Suppl 1:173.
52. Stallone JN, Crofton JT, Share L. Sexual dimorphism in vasopressin-induced contraction of rat aorta. Am J Physiol 1991;260:H453-8.
53. Stakisaitis D, Daugirdas JT. Sexual dimorphism of chloride transport in rat VSMCs. J Hypertension 1996;9:A22.
54. St-Louis J, Parent A, Lariviere R, Schiffrin EL. Vasopressin responses and receptors in the mesenteric vasculature of estrogen-treated rats. Am J Physiol 1986;251:H885-9.
55. Zhang J, Webb JG. Vasopressin enhances agonist-stimulated cAMP formation in vascular smooth muscle cells by a V1-receptor mechanism. FASEB J 1995;9:A613.
56. Stone JD, Crofton JT, Share L. Sex differences in central cholinergic and angiotensinergic control of vasopressin release. Am J Physiol 1992;263:R1030-4.
57. Mayinger B, Hensen J. Nonpeptide vasopressin antagonists: a new group of hormone blockers entering the scene. Exp Clin Endocrinol Diabetes 1999;107:157-65.
58. Ellis KJ, Vaswani A, Zanzi I, Cohn SH. Total body sodium and chloride in normal adults. Metabolism. Clin Experiment 1976;25:645-54.
59. Kennedy NS, Eastell R, Smith MA, Tothill P. Normal levels of total sodium and chloride by neutral activation analysis. Physics Med Biol 1983;28:215-21.
60. Wolf G. Refined salt appetite methodology for rats demonstrated by assessing sex differences. J Compar Physiol Psychol 1982;96:1016-21.
61. Stricker EM, Thiels E, Verbalis JG. Sodium appetite in rats after prolonged sodium deprivation: a sexually dimorphic phenomenon. Am J Physiol 1991;260:R1082-8.
62. Chow SY, Sakai RR, Witcher JA, Adler NT, Epstein AN. Sex and sodium intake in the rat. Behav Neurosc 1992;106:172-80.
63. Mensink GB, Arab L. Relationship between nutrient intake, nutritional status and activity levels in an elderly and in a younger population: a comparison of physically more active and more inactive people. Zeitschrift Gerontologie 1989;22: 16-25.
64. Speedy DB, Noakes TD, Rogers IR, Thompson JM, Campbell RG, Kuttner JA, et al. Hyponatremia in ultradistance triathletes. Med Sci Exerc 1999;31:809-15.
65. Ganong CA, Kappy MS. Cerebral salt wasting in children. The need for recognition and treatment. Am J Dis Child 1993;147:167-9.
66. Dyer AR, Stamler R, Grimm R, Stamler J, Berman R, Gosch FC, et al. Do hypertensive patients have a different diurnal pattern of electrolyte excretion? Hypertens 1987;10:417-24.
67. Adams-Campbell LL, Nwankwo MU, Ukoli FA, Janney C. Sex and ethnic differences associated with urinary sodium and potassium in African-American US white and Nigerian college students. J Hum Hypertens 1993;7:437-41.
68. Beard TC, Eickhoff R, Mejglo ZA, Jones M, Bennett SA, Dwyer T. Population-based survey of human sodium and potassium excretion. Clin Exper Pharmacol Physiol 1992;19: 327-30.
69. Yamori Y, Nara Y, Mizushima S, Mano M, Sawamura M, Kihara M, et al. International cooperative study on the relationship between dietary factors and blood pressure: a preliminary report from the Cardiovascular Disease and Alimentary Comparison (CARDIAC) Study. The CARDIAC Cooperative Study Research Group. Nut Health 1992;8:77-90.
70. Elliot P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al. Intersalt revisited: further analysis of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. BMJ 1996;312:1249-53.
71. Biosca G, Sanchez GR, Fernandez-Cruz A, Mizushima S, Wara Y, Yamori Y. Menopause status and blood pressure. WHO Cardiac Study. Oslo; 1993. p. 194.
72. Elliott P, Dyer A, Stamler R. The INTERSALT study: results for 24 hour sodium and potassium, by age and sex. INTERSALT Co-operative Research Group. J Hum Hypertens 1989; 3:323-30.
73. Staessen J, Bulpitt CJ, Fagard R, Joossens JV, Lijnen P, Amery A. Salt intake and blood pressure in the general population: a controlled intervention trial in two towns. J Hypertens 1989;6: 965-73.
74. Dawson-Hughes B, Fowler SE, Dalsky G, Gallaghter C. Sodium excretion influences calcium homeostasis in elderly men and women. J Nutrition 1996;126:2107-12.
75. Smith JB, Wade MB, Fineberg NS, Weinberger MH. Influence of race, sex, and blood pressure on erythrocyte sodium transport in humans. Hypertens 1988;12:251-8.
76. Taylor EA, Goh CR, Oh VM. Influence of family history of

cryptogenic hypertension, age, sex and race on lymphocyte sodium/potassium pumps. Ann Acad Medicine Singapore 1991;20:308-13.
77. Trevisan M, Krogh V, Cirilo M, Laurenzi M, Dyer A, Stamler J. Red blood cell sodium and potassium concentration and blood pressure. The Gubbio Population Study. Ann Epidemiol 1995;5:44-51.
78. Adeeb N, Ton SH, Muslim N. Effect of age, weight, race and sex on blood pressure and erythrocyte sodium pump characteristics. Clin Experim Hypertens 1990;12:1115-34.
79. M'Buyamba-Kabangu JR, Lijnen P, Lommelen L, Laermans M, Piccart Y, Tshiani KA, et al. Physiologic variability of erythrocyte concentrations and transport of sodium and potassium. Presse Medicale 1986;5:871-75.
80. Linjen P, M'Buyamba-Kabangu JR, Fagard R, Stassen J, Amery A. Erythrocyte concentrations and transmembrane fluxes of sodium and potassium in essential hypertension: role of intrinsic and environmental factors. [Review]. Cardiovasc Drugs Ther 1990;4 Suppl 2:321-33.
81. Tokudome G, Tomonari H, Gardner JP, et al. Variations in the apparent pH set point for activation of platelet Na^+-H^+ antiport. Hypertens 1990;16:180-9.
82. Mackovic M, Zimolo Z, Burckhardt G, Sabolic I. Isolation of renal brush-border membrane vesicles by a low-speed centrifugation; effect of sex hormones on Na+/H+ exchanger in rat and mouse kidney. Biochim Biophys Acta 1986;862:141-52.
83. Monagham JC, Fleming CL, Stokes GS. Effects of 17 alpha-ethinylestradiol in vitro on erythrocyte cation transport in men and women. Clin Exp Hypert Theor Practice 1991;A13:53-63.
84. Galley ED, Bean C, Grigg R, Sauders DM. The effect of cyclical hormonal changes on erythrocyte electrolyte transport mechanisms. Clin Sci 1986;70:263-9.
85. Monagham JC, Willcocks DA, Sinosich MJ, Stokes GS. Erythrocyte cation fluxes during the menstrual cycle in normal female subjects. Clin Sci 1987;73:223-6.
86. Fraser CL, Sarnacki Ph. Na^+-K^+-ATPase pump function in rat brain synaptosomes is different in males and females. Am J Physiol 1989;257:E284-9.
87. Guerra MA, Castillo RD, Battaner E, Mas M. Androgens stimulate preoptic area Na^+, K^+-ATPase activity in male rats. Neurosci Lett 1987;78:97-100.
88. Labella FS, Bihler I, Templeton J, Kim RS, Hnatowich M, Rohrer D. Progesterone derivatives that bind to the digitalis receptor: Effects on Na^+,K^+ ATPase and isolated tissues. Federation Proc 1985;44:2806-11.
89. Gallery ED, Bean C, Grigg R, Saunders DM. The effect of cyclical changes on erythrocyte electrolyte transport mechanisms. Clin Sci 1986;70:263-9.

Received 1 March 2004, accepted 15 September 2004
Straipsnis gautas 2004 03 01, priimtas 2004 09 15