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

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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...
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 inhibitors, selective serotonin reuptake inhibitors 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 pathogenic 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 osmodyrsregulation (42).

Association of hyponatremia and increased concentration of serum antiuretic 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 V₁ receptors (47). It has been shown that AVP-induced brain edema is mediated by the AVP V₁ receptor (49).

AVP through stimulation of V₁ 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 V₁ receptors, because the effect of AVP was completely inhibited by the V₁ 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).

\textbf{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 excreted 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).

\textbf{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⁺] 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⁺] 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).

\textbf{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 pH₁ set point of activation of the Na⁺/H⁺ antiport: men demonstrated an alkaline shift in the pH₁ 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).

\textbf{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], concentration and the number of Na+, K+-ATPase sites per erythrocyte and between the ouabain-sensitive sodium efflux per site and [Na], (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 86Rb 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.

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**Su lytimi susiję natrio apykaitos skirtumai, vaistų sukelta hiponatremija**

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**Raktas:** hiponatremija, natrius, lyties skirtumai, nepageidaujamų vaistų poveikis.

**Santrauka.** Straipsnyje pateikta literatūros duomenys apie su lytimi susijusius natrio (Na+) metabolizmo, Na+ pernašos per ląstelės membraną (Na+/H+ pasikeitimo, Na+/K+/2Cl− pernašos, Na+, K+-ATPazės), 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 gydymo (karbamazepinas, okskarbazepinas, tiazidai, antidepresantai ir kiti), gali sukelti hiponatremiją, kuri dažnesnė moterims. Šių skirtumų kilmė ką kas neišaiškė. Eksperimentiniai tyrimai su abiejų lyčių klinikinės studijos galia padėti atsakyti į klausimą, kodėl moterims dažniau išsivysto hiponatremija, ir rasti efektyvius hiponatremijos profilaktikos bei gydymo metodus.

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