# Sodium and Depression: Hypothetical Associations

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**ÖZET:**
Sodyum ve depresyon: hipotetik ilişkiler

Sodyum hücre dışı beden sıvısında bulunan önemli bir katyon ve sinir iletimi için gerekli olan bir elektrolittir. Serum sodyum konsantrasyonu vasopressin tarafından kontrol edilir. Vasopressin depresyon patofizyolojisinde de önemli rol oynamaktadır. Depresyonunun artmış rezidüel sodyum (hücre içi ve az miktarda kemikte bulunan sodyum) miktarıyla ilişkili olduğu, tedavi sonrası normal seviyelere döndüğüne ilişkin bazı bulgular mevcuttur. Bu yazıda sodyum ve depresyon arasındaki hipotetik ilişkiler ele alınmıştır.

**Anahtar sözcükler:** Depresyon, sodyum, vasopressin, dopamin, tiroid hormonları

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**ABSTRACT:**
Sodium and depression: hypothetical associations

Sodium is the major extracellular cation in body fluids and an essential electrolyte for the transmission of nerve impulses. Serum sodium concentration is controlled by vasopressin (AVP). AVP may play an important role in the pathophysiology of depression. There is also some evidence suggesting that depression is associated with a considerable increase in residual sodium, which returns to normal after recovery. This paper aims to present the relationship between sodium and depression.

**Key words:** Depression, sodium, vasopressin, dopamine, thyroid hormones

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## INTRODUCTION

Sodium is the major extracellular cation in body fluids and therefore has an important role in maintaining water balance within cells (1). Sodium is an essential electrolyte for the transmission of nerve impulses (2). Serum sodium concentration ($Na^+$) has very narrow limits of 138-142 mmol/L despite great variation in water intake (3). Any extra sodium is excreted by the kidneys (2).

### Control of serum sodium

Serum sodium concentration and thus serum osmolality are closely controlled by water homeostasis, which is mediated by thirst, arginine vasopressin (AVP, also known as vasopressin or antidiuretic hormone (ADH)), and the kidneys. Thirst and ADH act in parallel to control plasma osmolality and sodium concentration. The physiology of thirst is a highly complex process that must be controlled by a variety of somatomotor, autonomic, and endocrine responses. Increases in plasma osmolality and decreases in plasma volume are the most important stimuli to increase thirst and vasopressin release (4).

### Vasopressin

Vasopressin is a hormone produced by the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus, producing an antidiuresis by enhancing water reabsorption in the collecting ducts of the kidney. One of the most important roles of AVP is to regulate the retention of water, thus concentrating the urine and reducing urine volume (4,5).

Arginine vasopressin (AVP) is released into the peripheral circulation from the posterior pituitary and is responsible for antidiuresis (5,6). The physiologic stimuli for release of vasopressin can be divided into osmotic and non-osmotic factors.

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99

Volume depletion is probably the most powerful non-osmotic stimulus; however, other factors such as temperature, emotion, and pain have been shown to produce an effect. Acetylcholine, norepinephrine, dopamine, the neuroactive peptides, and opiates are neurotransmitters that are known to mediate this effect, although the role of each has not been fully elucidated (6).

## Vasopressin and Depression

In the central nervous system (CNS), AVP acts as a neuromodulator in a group of CNS-mediated functions such as learning and memory, social behaviors, circadian rhythmicity, thermoregulation, and autonomic functions. AVP is also known to directly modulate corticotropin-releasing hormone (CRF) leading to adrenocorticotropic hormone (ACTH) release and activation of the hypothalamic–pituitary–adrenal (HPA) axis (5,6).

Dysregulation of the HPA axis is believed to play a crucial role in the pathophysiology of depression (7,8). Studies of HPA function in depression reveal numerous abnormalities. These abnormalities include cortisol escape from dexamethasone suppression and increased cortisol responses to the dexamethasone corticotropin releasing hormone (DEX-CRH) test (8,9). The activation of the HPA axis is essential for an appropriate biological response to a stressful event. AVP and CRH are the major hormones of the HPA axis and both peptides are required for maximal pituitary–adrenal stimulation. AVP has ACTH- releasing properties, a response which may be dependent on the ambient endogenous CRH level. Following the combination of AVP and CRH, a much greater synergistic ACTH response is seen. Monoamine neurotransmitters that play a role in depression pathophysiology also have an important effect on HPA activity (8,10). Moreover, selective serotonin re-uptake inhibitors (SSRIs) have an effect on the regulation of the HPA system (decreased DEX-CRH test response). It has been found that plasma levels of the HPA axis hormones, corticosterone and ACTH, decreased after 15 days treatment with citalopram (9).

Some evidence suggests that the hypothalamo-hypophyseal neuropeptide, AVP, is involved in mood disorders (5,11). Central AVP-mediated functions such as attention, memory, nociception, and circadian rhythms are frequently disturbed in affective disorders. The suprachiasmatic nuclei (SCN) are thought to be involved in the regulation of circadian rhythms and contain AVP-synthesizing neurons. These neurons project exclusively inside the CNS and do not contribute directly to changes in plasma concentrations of AVP. However, AVP-containing neurons of the SCN do project to the paraventricular region of the hypothalamus and can therefore indirectly influence the resulting plasma levels of AVP. AVP and AVP-mediated functions may be a factor in the clinical picture of depression, possibly by influencing the activity of the HPA axis (5,11).

Increased vasopressinergic activity has been reported in patients with depression. Many studies have shown higher mean plasma AVP concentrations in depressed patients than in controls. Furthermore, increased plasma AVP levels were related to psychomotor retardation and have a significant inverse relationship with neuroticism (5,11). It has been suggested that high levels of AVP and subsequent down-regulation of AVP receptors may be the key biological abnormality in major depressive disorder. The data supports the hypothesis that AVP causes release of ACTH and subsequent release of cortisol from stimulated adrenal glands (10).

The mechanism of increased AVP plasma concentration in major depression is not well understood (11). Some authors suggest that higher levels of plasma AVP in depressive patients were caused by increased plasma osmolality. Another possibility that may play a role in the mechanism of increased plasma AVP levels in major depression is a lower serum prolyl endopeptidase (PEP), a serine proteinase that degrades substrates such as AVP. Thus, lower PEP activity may lead to increased concentrations of AVP. It could be possible that under the influence of (repeated) stress, increased synthesis of AVP and CRH is evoked, and that this production of central AVP is paralleled by a release of AVP in the general circulation (11).

In response to stress, the activation of the HPA

axis serves to restore homeostasis. Hypothalamic CRF/AVP release and pituitary ACTH secretion play a central role in regulating the stress response. Repeated stress is known to increase AVP expression in paraventricular CRF. There is evidence to support this association in depressed subjects. On the other hand, CRH and AVP stimulate ACTH synthesis and the principle function of ACTH is to stimulate cortisol release. AVP-stimulated ACTH secretion may be refractory to glucocorticoid feedback. It has been suggested that AVP is the primary regulator of the HPA axis in chronic stress. This condition may explain hypercortisolemia in depression (10).

The central vasopressinergic system has been examined for psychiatric drug development, including depression. This has led to the hypothesis of the utility of central vasopressinergic receptor antagonism as a potentially novel antidepressant strategy (6).

## Disorders of Sodium Metabolism in Depression

Some authors have suggested that abnormalities in electrolyte metabolism may cause mood changes and studies of the metabolism of electrolytes in affective disorders have demonstrated some relationships between the metabolism of electrolytes and affective disorders (12,13). These studies have shown that both depression and mania are related to changes in the plasma sodium concentration. In some cases rapid mood changes are also related to changes of sodium and water metabolism. The first studies in depressive patients derived from the old observation that urinary output tended to be low in depression and high in mania. More detailed study of the rate of urine flow during the changeover from depression to mania showed that an abrupt increase in urine flow actually preceded the mood change (12).

It is well known that lithium salts are effective in the treatment of mania and depression. The effects of lithium treatment on the distribution of electrolytes suggests that changes of sodium may be of great importance in the etiology of affective disorders. Lithium carbonate alters sodium transport and distribution (14).

There is some evidence that depression is associated with a considerable increase in residual sodium (intracellular and a small amount of bone sodium), which returns to normal after recovery (10,11). The rise of the residual sodium in depressive patients is illustrated by the ratio of sodium in the extracellular water to residual sodium (14). Decreased excretion of sodium in individuals during periods of depression has also been reported (13). If sodium retention is a feature of the early stages of depression, and if such retention persists during the illness, diuresis of sodium would be expected to accompany recovery (12).

The researchers have been able to demonstrate significant relationships between measures of the degree of verbal retardation in depressed patients and both the sodium/potassium ratio in the urine and specified frequencies in the EEG. In a later study researchers have found that certain EEG frequencies were also related to changes in both sodium balance and the concentration of sodium in the plasma in patients with depression (13). Similiar changes have also been reported in patients with periodic catatonia. Moreover, it was found that electroconvulsive therapy (ECT) caused a slight and quite transient retention of water and sodium (12).

Changes in water and electrolytes in depressive patients are not the result of vegetative symptoms of depression. Depression can decrease the appetite and can cause a considerable amount of weight loss. In a study in patients given a mixed diet, with a constant fluid intake, 12-hour urine collections were made over a period of several months. The result of the study showed that patients retained sodium and water during the depressive phases (12). Another study found a transient retention of water and sodium in patients with depression, but over the course of the whole illness there appeared to be no overall gains or losses (13). These studies suggest that the changes of serum sodium level can cause depression (12,13).

These results support the hypothesis that depression is accompanied by retention of sodium, which is excreted during recovery. The investigations reviewed above provide suggestive but equivocal evidence of some abnormalities of water and

sodium metabolism in depressive illness. If further work establishes that such abnormalities frequently occur, there remains the question of the relationship between the change in mood and the metabolic changes (12,13).

## Relationship Between The Sodium and Dopaminergic Systems

Dopamine (DA), released from the neurons of the substantia nigra pars compacta into the striatum, plays an important role in regulating normal and abnormal behaviors (15). Moreover, dysfunctions of dopaminergic neurotransmission are involved in the pathophysiology of various neuropsychiatric disorders including Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, drug abuse and depression (15,16).

Multiple sources of evidence support a role for diminished dopaminergic neurotransmission in major depression. Data from animal studies, human biological and postmortem studies and the action of antidepressant medications have shown the role of DA in depression (17). The mesocorticolimbic dopamine system is involved in motivation, psychomotor speed, concentration and the ability to experience pleasure, and impairments of these functions are prominent features of depression (17). Furthermore, reward is mediated by dopaminergic projections to the nucleus accumbens, suggesting that this neurocircuitry plays a crucial role in the pathogenesis of depression (18). Animal models of depression demonstrate altered mesolimbic DA system function, and moreover, many antidepressants enhance DA transmission (17). DA antagonists also reduce motivation and mood and induce states of depression (19). Investigations of cerebrospinal fluid metabolites, such as the DA metabolite homovanillic acid, reveal low levels in patients with major depressive disorder (20).

Dopamine is a biogenic monoamine and an important catecholamine neurotransmitter in the area of the thirst center in the lateral hypothalamus. In animals, a hyperdopaminergic state is associated with increased fluid intake, which can be reversed by dopamine antagonists (21).

Dopamine of renal origin plays a crucial role in the regulation of renal sodium. Dopamine exerts natriuretic and diuretic effects by activating dopamine receptors located at various regions in the nephron. The major consequence of the activation of dopamine receptors is the decrease of sodium reabsorption by the inhibition of proximal tubular luminal sodium transport. The Na-K-ATPase and the Na/H exchanger are the two major proximal tubule Na transport systems (22).

The renal dopaminergic system appears to be highly dynamic with many factors involved in its regulation. Dopamine modulates various renal functions including renal blood flow, glomerular filtration rate, tubuloglomerular feedback, renin release and renal reabsorption of sodium (23). A positive correlation has been reported between sodium intake and renal dopamine production. Urinary dopamine level, which may reflect the renal production of dopamine, is increased in response to high salt (sodium chloride) intake. Enhanced dopamine synthesis and release contribute to the natriuretic response. Dopamine receptors reduce tubular sodium reabsorption by inhibition of two main transport systems (22).

In the kidney, dopamine is synthesized by renal proximal tubule cells. The DA precursor L-DOPA enters into the cells by a sodium coupled transporter and is converted to DA by aromatic amino acid decarboxylase (AAAD). Once dopamine is synthesized, it is transported out of the cells where it can interact with dopamine receptors. Dopamine secretion depends in part on the activity of monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), the enzymes responsible for degradation of catecholamines. Inhibition of these enzymes, which are abundant in tubule cells, is increased by renal dopamine (22).

## Thyroid Hormones and Kidney Functions

Abnormalities of the hypothalamic-pituitary-thyroid (HPT) axis have been linked to depressive

disorders. Various authors have reported decreased serum thyrotrophin (TSH), a blunted TSH response to thyrotrophin releasing hormone (TRH) and increased serum free thyroxine (FT4) (24). They also provide evidence of a significant relationship between thyroid insufficiency and depression. Hypothyroidism is highly prevalence among depressed patients. Subclinical thyroid deficiency, which has few or no symptoms, is defined as abnormally high TSH with normal thyroid hormone levels and has been found in depressive patients at frequencies four times that of normal populations. Furthermore, thyroid hormones have been used in the treatment of depression (25).

There is a well-known interaction between the thyroid gland and kidney functions. Thyroid hormones (TH) are essential for the growth and development of the kidney and play an important role in regulation of water and electrolyte balance. Thyroid dysfunction causes remarkable changes in glomerular and tubular functions and electrolyte and water homeostasis. Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability to excrete water. The kidneys are also involved in the metabolism and elimination of TH. The decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH (26).

Thyroid hormones also influence the levels of water and electrolytes in different body compartments. A decrease in TH activity results in a significant decrease in fluid loss. This effect is not due to inadequate suppression of vasopressin release, or decrease in the reabsorptive ability in the kidney tubule, but rather to a reduction in the glomerular filtration rate (GFR) (27).

Thyroid hormones play an important role in the modulation of tubular transport of sodium. They have an effect on the sodium retention via the sodium–potassium ATP pump (Na/K ATPase). It has been showed that tubular reabsorption of Na is lower in thyroidectomized rats than in controls and that Na absorption increased in euthyroid rats treated with triiodothyronine (T3) (28).

## Antidepressant Drug-Induced Hyponatremia

Hyponatremia is defined as a Na serum level of less than 135 mEq/L and is the most common electrolyte disorder (29). Psychotropic agents have often been implicated in the causation of hyponatremia, including both antidepressants (tricyclics, selective serotonin reuptake inhibitors [SSRIs], and monoamine oxidase inhibitors) and antipsychotic drugs (phenothiazines and butyrophenones) (30). The prevalence of hyponatremia associated with SSRI and SNRI use varies from 0.5–32% (29). This discrepancy in the prevalence rates might be related to underdiagnosis, as low plasma sodium can be clinically asymptomatic (31).

The mechanism by which these drugs cause hyponatremia is believed to be the development of syndrome of inappropriate antidiuretic hormone secretion (SIADH) (30). However, the mechanism of action responsible for antidepressant-induced SIADH is not known. One of the possible mechanisms is the serotonin stimulatory effect of antidiuretic hormone secreted from the posterior pituitary gland, which is mediated by the 5HT2 and 5HT1 receptors (31). This syndrome consists of faulty urine dilution in the presence of plasma hyposmolality (32).

## CONCLUSION

There is no direct evidence for a link between sodium and depression, but indirect evidence suggests that sodium and depression might be closely associated with each other and these results may help further understanding of the issue. This paper presents baseline study findings, including a summary of major documents needed for reference.

Klinik Psikofarmakoloji Bülteni, Cilt: 23, Sayı: 1, 2013 / Bulletin of Clinical Psychopharmacology, Vol: 23, N.: 1, 2013 - www.psikofarmakoloji.org

103

# References:

1. Fereidoun H, Bahram A, Sadraddin KS, Akbari Abbass, Pouria H. Function of ADH and thirst mechanisms in the face of consuming salty water in male wistar rat. Pak J Physiol 2007;3(1):1-4.

2. Anderson J, Young L, Long E, Prior S. Sodium in the Diet. Food and Nutrition Series, Health 2007.

3. Kumar S, Berl T. Sodium. Lancet 1998;352(9123):220-8.

4. Rigss AT, Dysken MW, Kim SW, Opsahl JA. A review of disorders of water homeostasis in psychiatric patients. Psychosomatics 1991;32(2):133-48.

5. Yang J, Pan YJ, Yin ZK, Hai GF, Lu L, Zhao Y, et al. Effect of arginine vasopressin on the behavioral activity in the behavior despair depression rat model. Neuropeptides 2012;46(3):141-9.

6. Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. NeuroRx 2005;2(4):590-611.

7. Vreeburg SA, Hartman CA, Hoogendijk WJG, Dyck RV, Zitman FG, Ormel J, et al. Parental history of depression or anxiety and the cortisol awakening response. Br J Psychiatry 2010;197(3):180-5.

8. O'Keane V, Frodl T, Dinan TG. A review of Atypical depression in relation to the course of depression and changes in HPA axis organization. Psychoneuroendocrinology 2012;37(10):1589-99.

9. Knorr U, Vinberg M, Hansen A, Klose M, Feldt-Rasmussen U, Hilsted L, et al. Escitalopram and Neuroendocrine Response in Healthy First-Degree Relatives to Depressed Patients – A Randomized Placebo-Controlled Trial. Plos One (2011);6(6):e21224.

10. Dinan TG. Scott LV. (Anatomy of melancholia: focus on hypothalamic–pituitary–adrenal axis overactivity and the role of vasopressin. J Anat 2005;207(3):259-64.

11. van Londen L, Goekoop JG, van Kempen GM, Frankhuijzen-Sierevogel AC, Wiegant VM, van der Velde EA, et al. Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsychopharmacology 1997;17(4):284-92.

12. Shaw DM. Mineral metabolism, mania, and melancholia. Br Med J 1966;2(5508):262-7.

13. Gibbons JL. Electrolytes and depressive illness. Postgrad Med J 1963;39:19-25.

14. Coppen A, Shaw DM, Malleson A, Costain R. Mineral metabolism in mânia. Br Med J 1966;1(5479):71-5.

15. Franken IH, Nijs I, Pepplinkhuizen L. Effects of dopaminergic modulation on electrophysiological brain response to affective stimuli. Psychopharmacology 2008;195(4):537-46.

16. Alcaro A, Huber R, Panksepp J. Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. Brain Res Rev 2007;56(2):283-321.

17. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007;64(3):327-37.

18. Stein DJ. Depression, anhedonia, and psychomotor symptoms: the role of dopaminergic neurocircuitry. CNS Spectr 2008;13(7):561-5.

19. Felten A, Montag C, Markett S, Walter NT, Reuter M. Genetically determined dopamine availability predicts disposition for depression Brain Behav 2011;1(2):109-18.

20. van Praag HM, Korf J, Schut D. Cerebral monoamines and depression. An investigation with the Probenecid technique. Arch Gen Psychiatry 1973;28(6):827-31.

21. Ellinas PA, Rosner F, Jaume JC. Symptomatic hyponatremia associated with psychosis, medications, and smoking. J Natl Med Assoc 1993;85(2):135-41.

22. Maurel A, Spreux-Varoquaux O, Amenta F, Tayebati SK, Tomassoni D, Seguelas MH, et al. Vesicular monoamine transporter 1 mediates dopamine secretion in rat proximal tubular cells. Am J Physiol Renal Physiol 2007;292(5):1592-8.

23. Bobulescu IA, Quiñones H, Gisler SM, Di Sole F, Hu MC, Shi M, et al. Acute Regulation of Renal Na+/H+ Exchanger NHE3 by Dopamine: Role of Protein Phosphatase 2A. Am J Physiol Renal Physiol 2010;298(5);1205-13.

24. Brouwer JP, Appelhof BC, Hoogendijk WJ, Huyser J, Endert E, Zuketto C, et al. Thyroid and adrenal axis in major depression: a controlled study in outpatients. Eur J Endocrinol 2005;152(2):185-91.

25. Thompson FK. Is there a thyroid-cortisol-depression axis? Thyroid Science 2007; 2:1-2.

26. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. Eur J Endocrinol 2009;160(4):503-15.

27. Emmanouel DS, Lindheimer MD, Katz AI. Mechanism of impaired water excretion in the hypothyroid rat. J Clin Invest 1974;54(4):926-34.

28. Katz AI, Lindheimer MD. Renal sodium- and potassium-activated adenosine triphosphatase and sodium reabsorption in the hypothyroid rat. J Clin Invest 1973;52(4):796-804.

29. Kim CS, Choi JS, Bae EH, Kim SW. Hyponatremia associated with bupropion. Electrolyte Blood Press 2011;9(1):23-6.

30. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis 2008;52(1):144-53.

31. Papelbaum M, Aguiar MC. Sertraline-induced hyponatraemia. Rev Bras Psiquiatr 2006;28(3):256.

32. Cury LH, Kitadai FT, Helou CM. Antidepressant-induced hyponatremia. Clinics (Sao Paulo) 2006;61(6):579-80.