

# Voltage-Gated Sodium Channels Dysfunction in Depression: The Hypothesis

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## ÖZ:

Depresyonda voltaja bağımlı sodyum kanallarının disfonksiyonu: Bir hipotez

Voltaj bağımlı sodyum kanalları nöronlarda sinyal iletimi, kas kontraksiyonu, hormon salınımı, kardiyak pacemaker ve nörotransmitter salınımı gibi birçok fizyolojik süreçte aksiyon potansiyelinin oluşumunda rol oynar. Trisiklik anti-depresanlar ve duloksetin gibi bazı antidepressanlar voltaj bağımlı sodyum kanallarını etkileyebilir. Kanalopatiler olarak da bilinen sodyum kanalı gen mutasyonları epilepsi, kronik ağrı, migren ve kardiyak aritmiler gibi bazı kalıtsal hastalıklara yol açabilir. Bu hastalıkların birçoğu depresyona benzer şekilde epizodik, ataklarla seyreden, ataklar arasında normal veya normale yakın bir işlevselliğe dönen, psikolojik stres faktörleriyle artış gösteren özelliklere sahiptir. Sodyum kanal gen mutasyonlarının ayrıca intihar girişimlerine yatkınlık, uyku bozukluğu, hipotalamo-hipofizer adrenal eksen disfonksiyonunu gösteren kortikosteroidlerin salınımının diurnal ritminde bozulma ile ilişkili olduğu gösterilmiştir. Voltaj bağımlı sodyum kanallarının nöromodülasyonu depresyonun patofizyolojine de katkıda bulunan cAMP-bağımlı protein kinaz A ve protein kinaz C aracılı nöroplastisite ve hücre yenilenmede (resilience) önemli rol oynar. Antidepresan ilaçlar ve somatik tedaviler (örneğin; elektrokonvülsif terapi ve transkranial manyetik stimülasyon) hücre direnci arttıran CREB (cAMP response element binding protein) ve BDNF (brain derived neurotrophic factor) gibi birçok nörotropinleri düzenler. Bu bulgular depresyonda voltaja bağımlı sodyum kanallarının disfonksiyonu hipotezini desteklemektedir.

**Anahtar kelimeler:** voltaja bağımlı sodyum kanalları, depresyon

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## ABSTRACT:

Voltage-gated sodium channels dysfunction in depression: the hypothesis

Voltage-gated sodium (Na<sup>+</sup>) channels (VGSCs) are responsible for action potential initiation and propagation in most electrically excitable cells which are implicated in a wide range physiological functions including neuronal signalling, muscle contraction, endocrine secretion, cardiac pacemaking, as well as neurotransmitter releases. VGSCs are targets for certain antidepressant drugs such as tricyclic antidepressant and duloxetine. Sodium channel gene mutations are associated with a variety of inherited diseases known as channelopathies such as epilepsy, chronic pain, migraine and cardiac arrhythmia. A common clinical features of many channelopathies are the paroxysmal symptoms, discrete attacks, usually precipitated by a physiologic stress, and most people return to normal or near normal function between attacks similar to depression. It has been demonstrated that sodium channel gene mutations are also associated with increased susceptibility to suicidal attempts, sleep disturbance, dysregulation of diurnal rhythm in corticosterone secretion indicating hypothalamic-pituitary-adrenal axis dysfunction. Neuromodulation of voltage-gated sodium channels plays an important role in regulating neuroplasticity and cellular resilience mediated by cAMP-dependent PKA and PKC that could contribute to pathophysiology of depression. Antidepressant drugs and somatic therapies (e.g., electroconvulsive therapy, and transcranial magnetic stimulation) regulate a number of neurotrophins such as cAMP response element binding protein and brain derived neurotrophic factor which have the potential to increase neuroplasticity and cellular resilience. These findings support the hypothesis that sodium channel dysfunction may be involved in the etiology of depression.

**Keywords:** voltage-gated sodium channel, depression

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## INTRODUCTION

Voltage-gated sodium (Na<sup>+</sup>) channels (VGSCs) are responsible for action potential initiation and propagation in most electrically excitable cells including neurons, muscle cells, and cardiac myocytes (1-3). Sodium channels consist of large transmembrane proteins which regulate the electrical signals by allowing Na<sup>+</sup> ions to flow in or out of the cell (4-6). The extracellular Na<sup>+</sup> levels (150 mmol/L) are higher than their intracellular levels (15 mmol/L) (3). VGSCs can be either open, closed or inactivated states generating spontaneous intrinsic activity or typically as a result of the plasma membrane potential changes (3,7). The open sodium channels produce electrochemical gradient sustaining the numerous biological, biochemical, and bioelectrical reactions that affect the homeostatic processes in the molecular level (3,7). The ion channel activities are implicated in wide range physiological functions including neuronal signalling, muscle contraction, endocrine secretion, sensory transduction, cardiac pacemaking, cell volume regulation and cell proliferation (6). They also play a fundamental role in neurotransmitter releases, and thus modulate excitatory and inhibitory synaptic inputs that determine the behavioral responses (7).

VGSCs are multisubunit protein complexes composed of a  $\alpha$  and  $\beta$  subunits that are created by multiple genes (7-9). Malfunction of these subunits has been associated with the different types of diseases, which can be classified as channelopathies that are related to disorders of membrane and/or network excitability (3,7,9). Most of them are genetic disorders that are caused by mutations in the genes encoding channel proteins. Some are autoimmune diseases in which the body produces antibodies against its own channel molecules (6). The ion channel dysfunctions have been identified to cause important episodic neurological or muscular diseases such as different types of epilepsy, migraine, episodic ataxia, periodic paralysis, as well as long QT syndromes (3,7).

### The Hypothesis

Sodium channel dysfunction may lead to a wide variety of pathologic processes that are responsible for the depressive symptoms in the Central Nervous System (CNS) (10). Both spontaneous and evoked ectopic discharges in the affected primary hyperexcitable neurons and also

maybe their hypersensitive neighbors are likely to be key factors in the pathogenesis of depression (10,11). These changes in neuronal excitability result in dysregulation of various intracellular signaling transduction cascades including cAMP, protein kinase A (PKA) and C (PKC) pathways that could contribute to neuronal hyperexcitability and pathophysiology of depression (4,12). These pathways can also affect certain hormones (Adrenocorticotrophic Hormone, ACTH), neurotrophic factors (Brain derived neurotrophic factor, BDNF), neuromodulatory peptides, and inflammatory mediators (prostaglandins) that have a role in the biology of major depression (4,13-15). It has been shown that some of these diffusible mediators increase Na<sup>+</sup> current density and neuronal firing without necessarily actual membrane potential changes (4). Moreover, the functional alterations in sodium channel can cause abnormalities in the regulation of neurotransmitter release (10).

The presence of trauma, vascular, and metabolic disorders, bacterial and viral infection, inflammation, autoimmune attack, genetic abnormalities, and neurotoxins are a risk factors for nerve fiber dysfunction and can lead to structural brain damage such as myelopathy, neuronal injury, axonal loss, gliosis, and vascular lesions (4). Injury and disease affecting CNS can alter cellular excitability and perhaps trigger sensitization as a cause of depressive episodes (4). Episodic abnormal ion channels and electrical activity start in the certain areas of the brain involved in mood, thinking, sleep, appetite and behavior often presenting with depressive symptoms (16). Inherited mutations of ion channel genes can lead to possible compensatory changes in other ion channels that have normal location and physiological function contributing to cell or circuit excitability. Sodium channel dysfunction which are influenced by both genetic and environmental factors may be linked to recurrent depressive disorders (16).

### Findings Supporting The Hypothesis

#### Antidepressant drugs, pain and depression

Voltage gated sodium channels are targets for several classes of clinically used drugs, e.g. local anaesthetics (such as lidocaine), some anticonvulsants (lamotrigine and carbamazepine), antiarrhythmics drugs, tricyclic antidepressant (TCA; amitriptyline) and duloxetine

(1,2,10,17). The sodium-channel blockers that prevent neuronal action potential propagation have an analgesic effect on the neuropathic and inflammatory pain (10,17). Although the primary mechanism of action of TCAs is the inhibition of neurotransmitter reuptake that relieve depressive symptoms; additionally, they have been known to effect on an ion channels (18). TCAs may cause alteration of cardiac conduction, which can lead to cardiac arrhythmias due to their sodium channel blocking effects in cardiac tissues (18,19). In addition to their antidepressant actions, TCAs and duloxetine have been used for the medical treatment of pain (17,18).

The pain is caused by tissue inflammation and nerve injury resulting from a complex immune response (10). The immune reactions could have a crucial contribution to activation and sensitization of nociceptor and the ectopic discharge generation through the production of proinflammatory cytokines and chemokines (10). Increased baseline sensitivity and excitability of primary sensory neurons may play a key role in hyperalgesia accompanying inflammation (5,10). The altered function of VGSCs is likely responsible for hyperexcitability of sensory neurons and pathologic pain sensation (5). Certain antidepressants such as TCAs and duloxetine are often used to treat neuropathic pain and fibromyalgia (17,20). These findings suggest that antidepressant drugs which have an analgesic block peripheral nerve sodium channels and transmission of electrical impulses which may contribute to their antihyperalgesic efficacy (2,17,20).

### **Sodium channelopathies and depression**

Sodium channel gene mutations are associated with a variety of inherited diseases known as channelopathies (5,16). Genetic forms of epilepsy, chronic pain, migraine headache, and neuromuscular diseases such as periodic paralysis, ataxia, and cardiac arrhythmia are linked to mutations in sodium channels (5,16,21). Mutations of brain type 1 sodium channel (Nav1.1), which is caused by loss of sodium current and excitability of GABAergic inhibitory interneurons lead to generalized epilepsy (21). It is well known that depression is the most common one of the psychiatric disorder in patients with epilepsy. Mutations of the peripheral sodium channel Nav1.7 have been shown to cause familial episodic pain syndrome (21). A common clinical features of many channelopathies are the paroxysmal symptoms, discrete attacks, usually precipitated

by a physiologic stress, and most people return to normal or near normal function between attacks similar to depression (16). Channelopathies can exhibit extensive phenotype variability and diverse clinical manifestations (16). These complex genomic disorders may also interact with another genes or environmental factors (16).

Genetic polymorphisms of sodium channels have been found to be associated with psychiatric and cognitive disorders such as autism spectrum disorders (ASDs), alcoholism mood disorders and Alzheimer's disease (9,16,22). The high rates of comorbid neuropsychiatric disorders including mood disturbance and epilepsy in people with ASDs suggest that these diseases share common genetic foundations (9). The genes encoding voltage-gated sodium channels as well as other important genes for neural plasticity and synaptic function have been reported ASDs and depressive mood disorders (9).

### **Results of experimental studies**

The SCN8A (sodium channel protein type VIII alpha subunit) encodes Nav1.6 which is one of the major voltage-gated sodium channels in human brain (23). Nav1.6 sodium channel is localized at nodes of Ranvier, dendrites, and synapses, especially in the cortical pyramidal neurons of the prefrontal cortex and hippocampus (23,24). It has been demonstrated that dysfunction of the SCN8A voltage-gated sodium channel leads to decreased neuronal excitability which is related to changes in the firing patterns in mice with different SCN8A mutations (23-25). Mutations of SCN8A can result in mild cognitive deficits, learning disabilities, behavioral abnormalities and increased susceptibility to suicidal attempts (23,24,26). Furthermore, heterozygous mice with null mutation of SCN8A exhibited elevated anxiety suggesting that SCN8A plays a critical role in emotional instability in mice (23-25). The authors also proposed that The SCN8A might be a potential susceptibility gene for bipolar disorder (23,24).

Neurobiological investigations of major depressive disorder have included the sleep-wake cycle (24). Sleep disturbance is one of the main symptoms of clinical depression. The hypothalamic-pituitary-adrenal (HPA) axis and corticosteroids have important roles in the pathophysiology of major depression. Heterozygous carriers of loss of function mutations in the mouse display robust impairment of sleep initiation and maintenance, dysregulation of diurnal rhythm in corticosterone secretion

indicating HPA axis dysfunction (24). These findings support the hypothesis that sodium channel dysfunction may be involved in the etiology of depression.

### Neuromodulation and somatic treatments in depression

Neuromodulation of voltage-gated sodium channels plays an important role in regulating neuroplasticity and cellular resilience (27). Phosphorylation of sodium channel mediated by cAMP-dependent PKA and PKC modulates voltage-dependent gating, releases neurotransmitters which acts through a G protein-linked receptors, and reduces peak sodium current in neurons (27,28). Activation of dopamine receptors (D1) reduces peak sodium current in hippocampal pyramidal neurons through phosphorylation of the sodium channel by PKA and PKC (28,29). In prefrontal cortex neurons, serotonin 5-HT<sub>2A/C</sub> receptor stimulation activates PKC and reduces sodium current (28). The lack of modulation of sodium channels (Nav1.6) by protein phosphorylation disrupts to modulation of neural excitability, firing pattern, and neurotransmitter release at the synaptic terminals (28). Deletion of Nav1.6 channels in knockout mice alters regulation of sodium current and dopamine activation (28).

Impairment of neuroplasticity and cellular resilience proposed to underlie the pathophysiology of mood disorders (30). It has been suggested that long term treatment for mood disorders can only be achieved by the use of psychotropic agents with neurotrophic and

neuroprotective effects (30,31). Lithium, valproate, and antidepressant drugs indirectly regulate a number of neurotrophins such as CREB (cAMP response element binding protein), BDNF (brain derived neurotrophic factor) (30,31). Somatic therapies for treatment resistant depression including ECT (Electroconvulsive Therapy), TMS (transcranial magnetic stimulation), VNS (vagus nerve stimulation), DBS (deep brain stimulation) are neuromodulation therapies which have the potential to increase neuroplasticity and cellular resilience enhancing the synaptic strength, and growth of adult neurons (32,33).

## CONCLUSION

In this paper, it has been hypothesized that depression is an electrochemical disorder. Voltage gated sodium channels have an important role in initiation and propagation of electrochemical stimulus in the brain. As is also understood from giving data, sodium channel are essential for brain functions including cognitive functions, mood, motivation, appetite, and sleep. In the normal state, homeostatic mechanisms maintain the stability in spite of internal or external environmental changes (stimulus). If a stimulus is relatively strong enough, failure to respond effectively to an inability maintain homeostasis can result in disease. The different causes of depression including stressful life events, poor social skills, maladaptive coping strategies can cause sodium channel dysfunction or vice versa.

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