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The new molecular targets for antidepressants

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The efficacy of depressive disorders treatment is insufficient. It is explained by an incomplete understanding of both pathogenesis of depression and antidepressants mechanism action. An improvement of the treatment efficacy of depression disorders is closely associated with complete knowledge of the pathogenesis of disorders and antidepressant mechanism of action. The effect produced by the first line of antidepressants prescribed currently in the clinical practice includes the accumulation of monoamines and prolonged activation of their membrane receptors. However, a decrease in the membrane receptors density evoked by prolonged activation of monoaminergic receptors is counteracted by the second line of antidepressant activity. It is associated with the expression of inducible regulatory protein S100A10 (p11) and its partners. In this review, the authors examined the structure and function of protein p11, its interaction with such proteins as annexin A2, Ahnak, chromatin-remodeling factor SMARCA3. The authors analyzed the influence of p11 on the membrane density of serotonin 5-HT1B and 5-HT4 receptors, metabotropic glutamate receptors 5, voltage-dependent potassium Kv3, and calcium Cav1.2 and 1.3 channels, that play an important role in both the effect of antidepressants and the pathogenesis of depression disorders. A systematic literature search was conducted in Scopus, Web of Science, MedLine, elibrary, and other databases.

Keywords: depression disorders, antidepressants, p11, membrane receptors, ionic channels..

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Новые молекулярные мишени действия антидепрессантов

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Эффективность лечения депрессивных расстройств недостаточна. Это обусловлено неполным пониманием как патогенеза депрессии, так и механизмов действия антидепрессантов. Повышение эффективности лечения депрессивных расстройств тесно связано с получением более полных представлений о патогенезе заболевания и механизмах действия антидепрессантов. Первая линия действия применяемых сейчас антидепрессантов — накопление моноаминов и длительная активация мембранных рецепторов. Однако снижению плотности мембранных рецепторов, обусловленному включением гомеостатических механизмов вследствие длительной активации рецепторов, противодействует вторая линия активности антидепрессантов. Она связана с экспрессией под действием антидепрессантов индуцибельного регуляторного белка S100A10 (p11) и его партнёров. В обзоре рассмотрены структура и функции белка p11, его взаимодействие с белками аннексином A2, Ahnak, регулятором хроматина SMARCA3. Проанализировано влияние p11 на мембранную плотность серотониновых 5-HT1B и 5-HT4 рецепторов, метаботропных глутаматных рецепторов 5, потенциалозависимых калиевых Kv3 и кальциевых Cav1.2 и 1.3 каналов, которые играют существенную роль как в действии антидепрессантов, так и в патогенезе депрессивных расстройств. Системный поиск литературы проводился по базам данных Scopus, WebofScience, MedLine, elibrary и другим.

Ключевые слова: депрессивные расстройства, антидепрессанты, p11, мембранные рецепторы, ионные каналы.

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Introduction

Major depressive disorder occurs with a lifetime probability of 20% to 25% in women, 7% to 12% in men. Despite seventy years of intensive research, the pathophysiology of this disorder is yet to be fully understood. Treatment of depression is complex since the effect comes with a great latency, is not universally observed, and the therapy has multiple adverse effects [1]. Apparently, treatment of depressive disorders must be made more effective, which requires a better understanding of its pathogenesis and antidepressant pharmacology.

There are different functional classes of antidepressants today: selective and non-selective inhibitors of serotonin, noradrenaline, and dopamine reuptake, as well as monoamine oxidase inhibitors; they amplify the signaling pathway of cAMP, increase the levels of Gas in neuron membranes, and activate adenylate cyclase-coupled monoamine receptors, which activates protein kinase A (PKA) in neuron cytoplasm and nuclei. PKA, calcium/calmodulin-dependent protein kinase type IV (CAMK4) and mitogen-activated protein kinases (MAPK) phosphorylate and activate CREB, a transcription factor that enables protein production. An increase in the activity of PKA, MAPK ERK1/2, and CREB on top of continuous administration of antidepressants results in higher levels of mRNA, neurotrophins, and growth factors. The latter enable normal neuron functional, synaptogenesis and neurogenesis in the dentate gyrus, as well as homeostatic processes in neural networks [2, 3].

Therefore, **the first line** affected by antidepressants consists of positively adenylate cyclase-coupled monoaminergic receptors, N-methyl-D-aspartate (NMDA) glutamate receptors, metabotropic glutamate receptors, M choline receptors, etc. Since chronic administration of monoaminergic antidepressants results in a long-term increase in the extracellular concentration of monoamines in the brain, membrane receptors respond naturally to disrupted homeostasis by reducing their density. However, such chronic treatment also produces interesting collisions: the change in the membrane density of the same receptors varies from region to region in the brain. For instance, the density and activity of 5-HT1A receptors decreases in the somato-dendritic synapses of raphe nuclei while increasing in the hippocampus and in the cortex, where the levels of 5-HT1B and 5-HT4 receptors rise as well. Membrane density of alpha2 adrenoreceptors decreases in the somato-dendritic synapses of the locus coeruleus while increasing in the neurons of forebrain structures, even though the density of beta adrenoreceptors decreases there [4].

The therapeutic effects of selective serotonin reuptake inhibitors (SSRIs), which are the most popular antidepressants today, come from activating 5-HT1B and 5-HT4 receptors. However, it remains unclear why the membrane density of these receptors increases rather than decreases whilst SSRIs persistently raise the levels of serotonin in the extracellular fluid. It has been discovered in the last decade that the phenomenon is a result of serotonin receptors interacting with the inducible regulatory protein p11 also known as S100A10, nerve growth factor-induced 42C, calpactin I light chain, annexin light chain [5].

p11, its functions and partners

The protein is a member of S100, a family of low-molecular-weight (11–12 kDa) acidic proteins. Its structure shown in Figure 1 has two EF hands binding Ca2+. A loop (a hinge) between the second and the third spiral enables the molecule to bend. The protein forms homodimers that can form heterotetramers with annexin A2, a cytoskeleton protein. Beside membrane receptors, p11 has been found to interact with Nav1.8, Kv, and H+ iron channels, with TRVP5 cation channels, as well as with the fragments: tissue plasminogen activator, phospholipase A2, etc. [5, 6].

Nevertheless, the role of p11 and its targets in the development of the depressive behavioral phenotype and in antidepressant effects remains unclear due to a multitude of contradictory facts. On the one hand, administering antidepressants, levodopa (an anti-Parkinson medication), and serotonin (5-HT) has been found to increase the levels of mRNA and p11 in the murine cortex and hippocampus, effects mediated by the signaling pathways of neurotrophins, receptor tyrosine kinase TrkB, and protein kinase ERK. On the other hand, pro-depressive glucocorticoids, interleukins, tumor necrosis factor, and interferons also increase the levels of p11 in the rodent cortex and hippocampus [7]. Besides, non-steroidal anti-inflammatory drugs (NSAIDs) have been found to inhibit the SSRI-induced increase in p11 and related behavioral effects whilst enhancing the same effects caused by other antidepressants [8]. It is assumed that the depressogenic effect-associated increase in p11 is likely a homeostatic brain reaction that counters the development of depressive disorders.

Total p11 knockout causes the brain and the body to lose this protein, which triggers the development of depressive behavioral phenotype as shown by a change in the results of a whole behavioral test battery; it is also associated with a reduced effect of antidepressants on

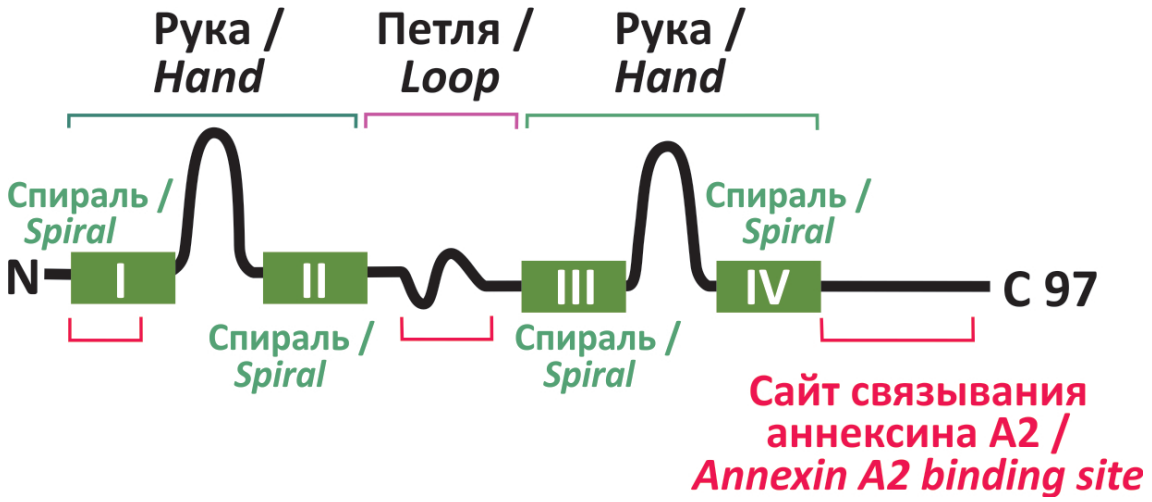

Figure 1. p11 structure. Roman numerals show spiralized molecule sites. The amino terminus to the left contains the site of binding to another p11 molecule, which is involved in forming a homodimer. The carboxyl terminus to the right contains the site of binding to annexin A2, which is involved in forming a heterotetramer.

Рисунок 1. Схематическое строение белка p11. Римскими цифрами отмечены спирализованные участки молекулы. Слева на амино-терминальном участке находится сайт связывания с другой молекулой p11 при образовании гомодимера. Справа карбокси-терминальный участок молекулы содержит сайт связывания аннексина A2 при образовании гетеротетрамера.

these indicators [9, 10]. Nucleus accumbens (NAcc) has been found to be the key structure involved in the development of depressive behavior in p11-deficient rodents. Indeed, suppressing p11 production in NAcc only by administering viral mRNAi reproduces all the signs of depressive behavior like total p11 knockout does. In intact mice, p11 levels in cholinergic NAcc interneurons are 30 times those in GABAergic medium spiny neurons; removal of p11 from cholinergic interneurons induces a depressive behavioral phenotype. On the contrary, excessive virus-associated p11 production in the same interneurons but not in dorsal striatum neurons eliminates behavioral disorders in total p11 knockout mice. Interestingly, p11 deficiency in cholinergic NAcc neurons does not diminish SSRI effects in mice when immobilized in tail suspension tests [11, 12]. Therefore, NAcc p11 is required to regulate emotions and mood, but not for antidepressants to have effect.

At the same time, p11 biosynthesis in cortical neurons is necessary for antidepressants to affect rodent behavior. For instance, chronic administration of antidepressants increases cortex and hippocampus p11 levels and boosts the expression of 5-HT4 receptors in p11-containing cortical murine neurons. Removing p11 from layer 5a projection neurons inhibits the behavioral effects of SSRIs and prevents the densifying of 5-HT4 receptors in neuron membranes whilst not affecting the signs of the depressive behavioral phenotype [9, 13].

How p11 Affects Serotonin and Glutamate Receptors of Membranes

Being a regulatory protein, p11 can by itself or in combination with other proteins interact with other target proteins and alter their activity. In the murine cortex, hippocampus, and NAcc, p11 is localized in close proximity to 5-HT1B/5-HT4 receptors in neuron membranes. p11 interacts with the third intracellular loop of serotonin receptors and increases their density in neuron membranes. This amplifies the cAMP-mediated signaling pathways of these receptors. However, p11 gene knockout suppresses the activity of 5-HT1B/4 receptors by reducing their density in neuron membranes [14, 15]. Therefore, p11 regulates membrane density rather than transcription and translation of serotonin receptors. In cultured cortical neurons, p11 enhances the effects of serotonin receptors on Ca2+ transmembrane current and protein kinase ERK1/2 activity. Serotonin and agonists of 5-HT1B receptors affect the phosphorylation of synapsin I, a presynaptic protein, and the corticostriatal glutamatergic synaptic transmission; these effects also depend on p11 [14].

Antidepressant-like effects of serotonin 1B and 4 receptor agonists in forced swim and tail suspension tests are weaker in p11 knockout mice compared to intact animals. The anxiolytic effects of these agonists are also reduced in p11-deficient mice subjected to open field tests [14]. 5-HT1B agonists have different effects on emotional learning in passive avoidance tests, disrupting

it in intact mice and boosting it in p11 knockout mice. Excessive p11 expression induced by viruses in dentate gyrus and in the CA1 region of the hippocampus caused emotional learning in p11 knockout mice to recover [16].

Studies of pyramidal corticostriatal neurons of the 5a layers of motor and sensory cortex in rats found that only some of these neurons expressed p11. These neurons have a higher electrical excitability compared to p11-negative pyramidal neurons; chronic administration of SSRIs increases the density of 5-HT2A rather than 5-HT4 receptors in the former. Stressogenic effects (chronic social isolation) reduced the density of 5-HT2A receptors in p11-positive pyramidal neurons whilst chronic administration of fluoxetine reversed this effect [15].

Aside from various serotonin receptors, p11 also interacts with cG protein-dependent metabotropic glutamate receptors (mGluRs). These receptors are divided into three groups: mGluR1 and mGluR5 in Group I, mGluR2 and mGluR3 in Group II, and mGluR4/6/7/8 in Group III. Behavioral studies found mGluR5 and mGluR2/3 blockers to have a rapidly developing antidepressant effect on mice. Besides, the mGluR5 cytoplasmic tail was found to have a p11 binding site consisting of a ser-thr-val amino acids sequence. Immunoprecipitation showed that p11/annexin A2 (Anxa2) heterotetramer was capable of binding to mGluR5. Testing on cultured HEK293 cell lines with embedded mGluR5 showed the effects of mGluR5 agonist to cause oscillations in the intracellular concentration of Ca2+, which would increase in case of excessive p11 production and decrease in case of damaged Anxa2. Therefore, p11/Anxa2 heterotetramers enhance the functioning of mGluR5. Further tests on the same cells, as well as on a COS-7 line, showed p11 and mGluR5 to co-increase their accumulation in cytoplasmic membranes, with p11 increasing the membrane density of mGluR5.

p11 and mGluR5 are found together in glutamatergic and GABAergic neurons. mGluR5 knockout in glutamatergic neurons prolonged the immobilization time in forced swim and tail suspension tests whilst reducing the sucrose preference, i.e., depressive behavioral phenotype progressed. The same procedure applied to GABAergic neurons caused an opposite change in behavior, i.e., it had an antidepressant-like effect. Similar results were obtained with p11 knocked out in GABAergic neurons. p11 knockout in glutamatergic neurons did not cause depressive behavior but made the mice more sensitive to chronic moderate stress. Another behavioral test (novelty-suppressed feeding) is used to characterize depressive and anxious behavior; this test found MPEP, an mGluR5 blocker, to have an antidepressant-like effect that would not manifest in p11 knockout mice. mGluR2/3 blocker also had an antidepressant-like effect, but that effect was not altered by removing p11. Therefore, the antidepressant-like effect of MPEP in intact mice could be eliminated by p11 knockout and reproduced by genetic deletion of mGluR5 in PV+ GABAergic interneurons [19]. The excitatory synaptic inputs of PV+ interneurons have effects that are known to stem from the activation of ionotropic AMPA and NMDA glutamate receptors, and mGluR5 increase the functional activity of NMDA receptors [20, 21]. Therefore, it can be assumed that the pharmacological or genetic suppression of mGluR5 activity inhibits the activity of PV+ GABAergic inhibitory interneurons and disinhibits glutamatergic pyramidal cortical and hippocampal neurons. Behavior-wise, this manifests itself as an antidepressant-like effect.

How p11 Affects Voltage-Gated Potassium and Calcium Channels

Beside serotonin and glutamate receptors, p11 also controls the membrane density and activity of potassium channels, which determines the excitability of neurons, as well as the duration and frequency of neural spike generation. In p11 knockout mice, the hippocampus was found to have suppressed transmembrane current through Kv3.1 potassium channels that are densely packed in the membranes of parvalbumin-positive (PV+) interneurons; this suppression was associated with a lower frequency of neuron discharge in response to depolarizing the membrane with a 100 pA step in inward current. HCN cation channel currents did not change under the same circumstances. Degradation and the resulting destruction of Kv3.1 channels caused a reduction of transmembrane currents in PV+ basket cells of the dentate gyrus. Besides, p11 knockout in dentate gyrus granule cells caused mice to have double the amplitude of GABAergic IPSPs due to optogenetic stimulation of PV+ interneurons. This was due to the loss of Kv3.1 channels in axon terminals of PV+ interneurons, which limit the duration of action potentials and the presynaptic release of GABA. p11 knockout in PV+ interneurons also caused more pronounced anxious behavior in a novel environment whilst compromising their resilience to depressogenic effects of protective social stress, even though sucrose preference and immobilization time in tail suspension tests did not change [22].

PV+ interneurons are important for cognition, emotions, learning, and memory. Emotional disorders, epilepsy, or schizophrenia can develop should these

neurons fail. In these neurons, Kv3 potassium channels accelerate spike repolarization and shorten the inter-spike interval; in presynaptic terminals of these neurons, Kv3 channels regulate GABA release and alter spike duration [23–25]. Interestingly, prefrontal and parietal cortical neurons have lower membrane density of Kv3.1 channels in schizophrenic patients; antipsychotics increase that density to health levels [26]. On the other hand, p11 knockout mice only had a lower density of Kv3.1 channels in hippocampus, but not in other brain structures, i.e. the mechanisms that control Kv3.1 density vary from structure to structure. Whilst chronic administration of antipsychotics increases the density of Kv3.1 channels in cortical structures, chronic administration of antidepressants reduces such density in the hippocampus. Chronically administered antidepressants have an inhibitory effect on Kv3.1 channels in PV+ dentate gyrus interneurons; this effect is associated with the activation of 5-HT5A receptors and PKA-induced phosphorylation of serine residue 503 in the Kv3.1b alpha subunit [27]. Therefore, it seems that the activity of Kv3.1 channels in PV+ interneurons is modulated by chronic administration of antidepressants, as it peaks early in treatment and is suppressed later on. Indeed, the initial effects of antidepressants cause the spike activity of PV+ interneurons to rise due to the activation of 5-HT1B receptors, a reduction in cAMP and in PKA activity, which reduces the phosphorylation of the Kv3.1 alpha subunit and boosts the functioning of Kv3.1 channels; however, the activity of these neurons attenuates further one due to down-regulation of Kv3.1 channels caused by the increased activity of 5-HT5A receptors [27].

Voltage-gated (VG) Ca2+ channels are another depression- and antidepressant-related molecular target of p11. Indeed, L type VG Ca29 channels enable the delivery of Ca2+ into neuron cytoplasm, activate CAMK4 and MAPK, and enhance the transcription processes. These channels are needed for neuron maturation, synaptic plasticity, and homeostasis of neural networks [28, 29]. Genetic research has shown that Cav1.2 (CACNA1C) polymorphism is associated with a higher risk of major depressive or bipolar disorders, or schizophrenia [29].

p11 interacts with serotonin receptors and potassium channels as a heterotetramer formed with Anxa2, a cytoskeleton protein. In turn, p11/Anxa2 can form a complex with the chromatin-remodeling factor SMARCA3. Knocking out the latter does not cause depressive behavioral phenotype to emerge and develop in mice; however, it mitigates the behavioral effects of SSRIs as well as their effects on neurogenesis [30]. p11/Anxa2 was later found to be able to form a complex with Ahnak, a high-molecular-weight (680 kDa) protein. This protein is involved in forming the gap junctions between epithelial cells in ventricular walls [30]. Ahnak was also found to be capable of binding to VG Ca2+ channel beta subunit in myocardiocytes and to be involved in regulating the density of Cav1.2 channels in the membranes of myocardiocytes, osteoblasts, and T cells [31, 32].

Biochemical studies on dentate gyrus and layers 2/3 of murine prefrontal cortex found Ahnak to stabilize the p11/Anxa2 complex; besides, the N-terminus of Ahnak interacts with the pore-forming L-type Ca channel alpha subunit, whilst the C-terminus interacts with the modulatory beta subunit of the same channel and with the p11/Anxa2 complex. Testing cultured embryo-derived cortical neurons revealed Ahnak knockout to reduce the total amplitude of Ca2+ currents by reducing the transmembrane current component associated with the activation of L-type calcium channels. Tests on the murine prefrontal cortex and hippocampus sections found layer 2/3 pyramidal neurons and PV+ interneurons of the dentate gyrus in Ahnak knockout mice to have reduced amplitude of calcium currents triggered by the activation of the Cav1.2 channels. Importantly, the total number of Cav1.2 and Cav1.3 alpha subunits and additional beta subunits would not change even in light of a 50% reduction in transmembrane currents. Consequently, triple protein complex p11/Anxa2/Ahnak regulates neuron membrane fixation of L-type calcium channels, but not the transcription or translation thereof [33].

Behavior-wise, Ahnak knockout mice had a depression-like phenotype manifesting as lower sucrose preference compared to water (a sign of anhedonia) and longer immobilization in swim and tail suspension tests. At the same time, local Ahnak knockout in glutamatergic neurons of the forebrain caused depression-like behavior in mice as indicated by a change in the behavioral test results. Local Ahnak knockout in PV+ interneurons had an antidepressant-like effect in sucrose preference and forced swim tests [33].

Interestingly, L-type Ca2+ channels regulate neuron excitability and spike generation. They employ several methods to this end: similarly to T-type Ca2+ channels (Cav3), L-type channel activation causes long-lasting depolarization of neuron membranes, which generates spikes; increased intracellular Ca2+ concentration activates BK channels, whilst depolarization excites VG Kv3.1 channels, and both types contribute to shortening the spikes while making them more frequent. This is why Ahnak knockout reduces the membrane density

of L-type channels in limbic glutamatergic neurons and suppresses their activity, causing a progressive depressive behavioral phenotype. On the other hand, local Ahnak knockout in PV+ interneurons suppresses their activity as well, but it also disinhibits cortical and hippocampal pyramidal neurons as is observed during the administration of fast-acting antidepressants: ketamine and mGluR5 blockers [34, 35].

Conclusions

In conclusion, it is safe to say the second line of antidepressant action comprises inducible regulatory proteins S100A10 (p11), annexin A2, etc., which can interact with membrane receptors and ion channels. Their intracellular carboxyl terminus or one of the intracellular loops contains a specific sequence of amino acids that determines the affinity to regulatory proteins. Besides, regulatory proteins can also interact with cytoskeleton elements. Complexes of these proteins regulate the transport of protein molecules and their fixation in membranes. Since chronic administration of antidepressants increases p11 levels in neurons, it causes a higher density of 5-HT1 and 5-HT4 receptors despite the homeostatic mechanism that has an opposite effect. On the other hand, serotoninergic and noradrenergic neurons of the afterbrain have low or no p11, causing a homeostatic response to antidepressants. That being said, complexes of p11, annexin A2, etc. stabilize and enhance the effects of monoaminergic and some fast-acting (e.g. mGluR5 blockers) antidepressants. Finally, total or local p11 knockout in the brain causes depressive disorders to progress, most likely due to disrupted fixation and change in the density of receptors and ion channels in neuron membranes.

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