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Targets of polyamine dysregulation in major depression and suicide: activity-dependent feedback, excitability, and neurotransmission

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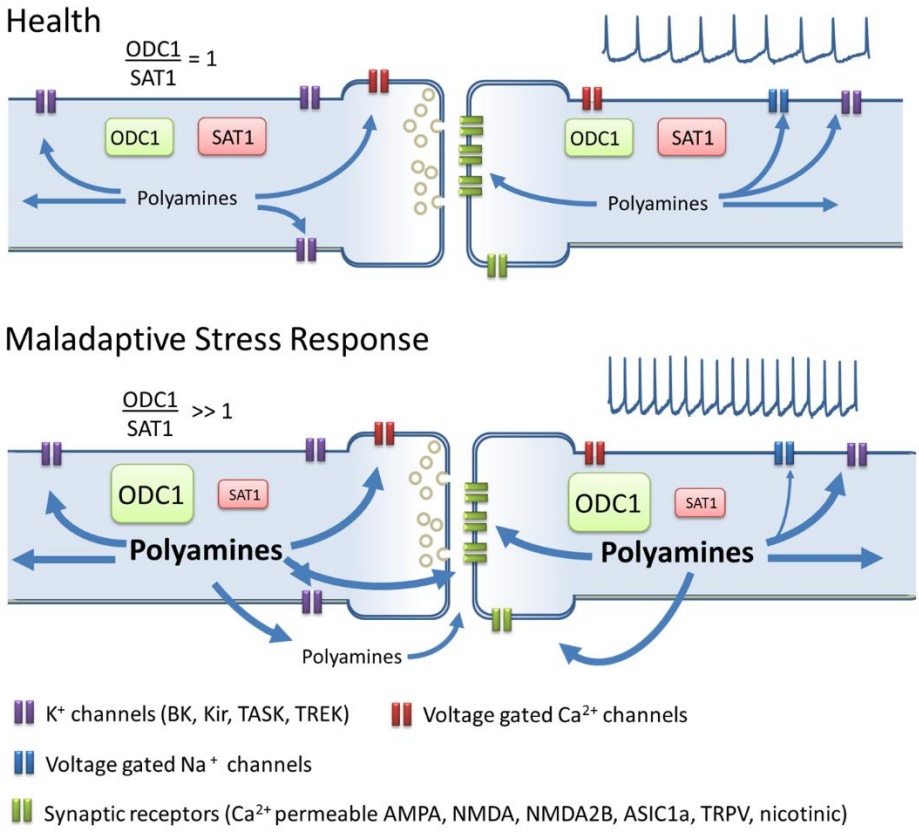
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Graphical Abstract



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Highlights

- Evidence of polyamine dysregulation in neuronal hyperexcitability in Major Depressive Disorder
- Table of extracellular and intracellular polyamine membrane targets involved in the control of neuronal excitability
- Examination of the polyamine system in activity-feedback mechanisms.
- Discussion of polyamines as mediators of allostasis in Major Depressive Disorder.

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Abstract

Major depressive disorder (MDD) is a leading cause of disability worldwide characterized by altered neuronal activity in brain regions involved in the control of stress and emotion. Although multiple lines of evidence suggest that altered stress-coping mechanisms underlie the etiology of MDD, the homeostatic control of neuronal excitability in MDD at the molecular level is not well established. In this review, we examine past and current evidence implicating dysregulation of the polyamine system as a central factor in the homeostatic response to stress and the etiology of MDD. We discuss the cellular effects of abnormal metabolism of polyamines in the context of their role in sensing and modulation of neuronal, electrical, and synaptic activity. Finally, we discuss evidence supporting an allostatic model of depression based on a chronic elevation in polyamine levels resulting in self-sustained stress response mechanisms maintained by maladaptive homeostatic mechanisms.

Keywords: Polyamine system, Major depression, suicide, excitability, homeostasis, ion channels, neurotransmitter receptors.

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Major depressive disorder (MDD) is a leading cause of disability worldwide (WHO, 2011). Multiple lines of evidence suggest that altered stress-coping mechanisms underlie the etiology of MDD by affecting neuronal communication in brain areas involved in the control of emotions and in stress response. Genetic and environmental factors, such as childhood trauma and chronic stress, can also increase the risk of developing MDD and may determine individual differences in response to diverse forms and durations of stress (Hammen, 2005; Hankin et al., 2007; Kendler et al., 1998; Tennant, 2002). Little is known about whether homeostatic mechanisms are affected in MDD stress response at the molecular level. In this review, we examine past and current evidence implicating a dysregulation of the polyamine system in MDD as a central factor in the etiology of MDD and in the homeostatic response to stress.

Polyamines (putrescine, spermidine, spermine, and agmatine) are ubiquitous, short, positively charged aliphatic amines that have fundamental roles in homeostatic mechanisms (Fig. 1). Their cellular roles include the regulation of gene transcription and post-transcriptional modifications, the modulation of synaptic activity, and the modulation of ion channels that participate in the excitability of neuronal networks (Table 1) and as reviewed by Pegg (Pegg, 2009)). Polyamine levels are tightly regulated by two key rate-limiting enzymes - Ornithine decarboxylase (ODC1) and Spermidine/Spermine N1-Acetyltransferase 1 (SAT1) (Fig. 2). ODC1 is the first enzyme in the synthesis of polyamines and produces putrescine from ornithine (Pegg, 2009); alternatively, putrescine can also be produced from agmatine by the enzyme agmatinase (AGMAT) (Sastre et al., 1996). Agmatine is also thought to be a neurotransmitter, with antagonistic effects at NMDA receptors and interactions with □2-adrenoreceptors (Reis and Regunathan, 2000), and has been shown to have antidepressant properties in animal models (Zomkowski et al., 2002), and in one clinical trial (Shopsin, 2013). Putrescine is the substrate to produce spermidine and spermine in sequential enzymatic reactions, while SAT1 is the rate limiting enzyme in the catabolism of polyamines (Pegg, 2009). Polyamine levels, particularly putrescine and agmatine, have been demonstrated to increase during stress, a phenomenon called the polyamine stress response (PSR) (Gilad and Gilad, 2003; Turecki, 2014). PSR magnitude is correlated with the intensity of the stressor and with the intensity of the behavioral

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response to stress, suggesting that a dysfunction of the polyamine system may be involved in the development of abnormal stress responses in conditions like MDD (Gilad and Gilad, 2003).

The effects of lithium in animal models and humans also evidence PSR alterations in MDD and suicide. Lithium is a commonly used mood stabilizer with significant anti-suicidal properties (Ahrens and Muller-Oerlinghausen, 2001; Bocchetta et al., 1998). Lithium has been shown to block PSR in the rodent brain when chronically delivered following dexamethasone treatment (Gilad and Gilad, 2003; Gilad et al., 1992b). A similar blockage of brain PSR is observed when lithium is administered pre or post the application of a stressful stimuli (Gilad and Gilad, 1996). Recently, Squassina and colleagues (Squassina et al., 2013) examined the effect of lithium on SAT1 gene expression in a cohort of lymphoblastoid cell lines which included cell lines from controls and subjects with bipolar disorder. The bipolar subjects were grouped into three suicide categories; suicide completers, high suicide risk and low suicide risk. Seven-day lithium treatment increased SAT1 gene expression for all groups except the suicide completers, suggesting differential regulation of SAT1 in suicide completers.

Gene expression studies in post-mortem human brains have consistently supported an alteration of the polyamine system in MDD and suicide. The first study suggesting a dysregulation of the polyamine system in MDD-suicides showed significant decreases in gene and protein expression of SAT1 in the precentral gyrus (BA4) and cortical frontal lobe areas (BA11 and BA8,9) in both non-depressed suicides and MDD-suicides compared to controls (Sequeira et al., 2006). This finding has been confirmed by our group and several others across brain regions and several population groups (Fiori et al., 2011; Guipponi et al., 2009b; Klempan et al., 2009a; Klempan et al., 2009b; Pantazatos et al., 2015; Sequeira et al., 2007). It was also demonstrated that the rs6526342 SNP, located in the promoter regulatory region of SAT1, had a significant effect on gene expression and that this SNP was associated with suicide in a French-Canadian sample (Sequeira et al., 2006), known to have a founder population effect (Scriver, 2001). The genetic effect of the rs6526342 SNP on brain SAT1 gene expression was confirmed in French-Canadian (Fiori et al., 2009) and Mexican (Tovilla-

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Zárate et al., 2015) cohorts but, not in more genetically heterogeneous European cohorts (Guipponi et al., 2009a), suggesting the presence of other genetic variants involved in the control of SAT1 gene expression. Other genetic association studies also showed an association between ODC1 SNPs (rs1049500 and rs2302614) and suicide attempts (Sokolowski et al., 2013). Ornithine decarboxylase antizyme 1, and 2 (OAZ1 and OAZ2), enzymes that control ODC1 activity by degradation (Fig. 2), have also been found to be upregulated in suicide completers across multiple psychiatric diagnoses including MDD (Gross et al., 2013). Moreover, gene expression of AMD1, which participates in the synthesis of spermidine and spermine from putrescine is altered in middle temporal cortex (BA21) of MDD individuals (Aston et al., 2005). Overall, these gene expression changes suggest abnormal concentrations of polyamines in MDD. Concordantly, putrescine and spermidine levels were significantly elevated in cortical areas (BA4, BA8/9, and BA11) of male MDD-suicide victims when compared to controls (Chen et al., 2010) and suggest that abnormal metabolism of polyamines might be involved in the pathophysiology of suicide and MDD by modulating stress response. Henceforth, we will discuss the polyamine system in the context of its role in sensing and controlling of neuronal electrical activity and its involvement in MDD and suicide.

Signatures of brain activity in MDD

Neuroimaging studies have shown that the strength of functional, reciprocal connectivity between the amygdala, a region critical in the generation and processing of negative emotions, and frontal cortical regions, which are involved in the modulation of amygdala reactivity and cognitive interpretation of negative stimuli, predicts successful emotional regulation (Banks et al., 2007; Comte et al., 2016; Hariri et al., 2002). Similar studies in people with MDD have shown amygdala hyperactivity at rest and during emotional and cognitive processing (Fales et al., 2008; Sheline et al., 2001; Siegle et al., 2002). In parallel, prefrontal cortex (PFC) areas like the left dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (ACC) and rostral cingulate show decreased activity at rest and fail to regulate amygdala hyper-reactivity during processing of negative stimuli (Davidson et al., 2002; Mayberg et al., 1999; Pizzagalli et al., 2006). Hyperactivity during resting state in ventral anterior midline regions, like perigenual ACC, ventromedial prefrontal cortex (VMPFC), ventral striatum, putamen and the

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dorsomedial thalamus in MDD is also observed in homologous regions of animal models of depression (Alcaro et al., 2010; Krishnan and Nestler, 2008; Shumake and Gonzalez-Lima, 2003), suggesting shared mechanisms across biological species (Alcaro et al., 2010).

Evidence of regional hyperactivity in MDD patients comes principally from imaging studies measuring increased metabolism via blood-oxygen-level dependent (BOLD) signal using functional Magnetic Resonance Imaging (fMRI) (Hasler and Northoff, 2011). Simultaneous measurements of the BOLD signal and electrophysiological data in non-human primates have shown that the BOLD signal mostly represents: 1) excitatory and inhibitory synaptic activity, 2) voltage-dependent membrane oscillations, and 3) spike after-potentials, generated by Ca^{2+}-activated K^{+} currents, that participate in the modulation of spiking frequency (Logothetis, 2003). In MDDs, the reported regional hyperactivity therefore most likely reflects enhanced firing rate and hyperexcitability of regions involved in stress response. Interestingly, MDD patients have 3 to 7-fold higher risk of developing epilepsy, and epilepsy itself increases the risk of developing MDD (Danzer, 2012; Forsgren and Nystrom, 1990; Hesdorffer et al., 2000; Kanner, 2011), supporting the idea that hyperexcitability is one of the key features of MDD.

In animal models, stress at early prenatal developmental stages increases the risk of seizures later in life due to hyperexcitability of the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis (Dube et al., 2015). Similarly, chronic stress produces depression-like behavioral changes in rodents (Rosenkranz et al., 2010) that correlate with unambiguous evidence of hyperexcitablity in lateral amygdala (LAT) neurons. Interestingly, this hyperexcitablity is better explained by reduction in the expression of Ca^{2+}-activated K^{+} channels than by the reduction of synaptic inhibitory control (Rosenkranz et al., 2010). In summary, neuronal excitability alterations suggest a dysregulation in activity-feedback mechanisms involved in the development of MDD.

Polyamines in activity-feedback mechanisms

While the role of polyamines on synaptic and ion channel modulation is well known, their role in activity-feedback mechanisms that control neuronal firing rate is somewhat less recognized. Evidence from the past three decades shows that firing rate and ODC1

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activity are tightly correlated across a broad range of excitability levels, from small changes of ODC1 occurring during physiological stimulation of visual pathways, to large increments (≥ 50-fold) during epileptiform activity (Baudry et al., 1986) or electrical stimulation (Bondy et al., 1987; Pajunen et al., 1978). Notably, even small changes in the concentration of polyamines during physiological stimulation can have important modulatory effects on excitatory synaptic inputs that modulate sensory experience (Aizenman et al., 2002), indicating that the polyamine system participates in activity-feedback mechanism that sense and regulate neuronal activity (Fig. 3).

How neuronal activity induces ODC1 is not clearly understood but in peripheral tissue there is evidence of a physiological coupling between polyamine levels and intracellular calcium (Ca^{2+}) concentrations (Chang, 1991; Koenig et al., 1987; Langdon et al., 1984). In a pioneer study of a phenomenon called the calcium paradox, Koening et al. linked Ca^{2+} and polyamines with excitability and pathological consequences of maladaptive homeostatic mechanisms in the heart (Koenig et al., 1987). Koening et al. (1987) demonstrated that changes in ODC1 activity and polyamine concentrations followed changes in intracellular Ca^{2+} concentration ($[Ca^{2+}]$) with a time delay of approximately 15 seconds. These series of experiments showed that ODC1 and polyamines are part of an activity feedback mechanisms involving intracellular $[Ca^{2+}]$, and that abnormal polyamine-mediated compensation may trigger pathological excitability, intracellular $[Ca^{2+}]$ overload, and cell death (Koenig et al., 1987). Similarly, in neurons, a reduction in extracellular $[Ca^{2+}]$ from 2 to 1 mM produces hyperexcitability and seizure-like activity (Isaev et al., 2012). Interestingly, a Ca^{2+} sensor receptor (CaSR) that is activated by both Ca^{2+} and spermine, inhibits the Na^{+} leak channel (NALCN), so when Ca^{2+} concentrations decrease, the CaSR can no longer inhibit the NALCN channel producing a continuous depolarizing Na^{+} current that increases excitability (Lu et al., 2010).

Induction of ODC1 by inflow of extracellular $[Ca^{2+}]$ has also been observed in lymphocytes (Otani et al., 1985), osteoblasts (Van Leeuwen et al., 1989), and pancreatic (Chang, 1991) and epithelial cells (Langdon et al., 1984). In cardiac cells, this ODC1 induction is caused by the activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2; also known as P42/P44 MAPK), and P13K/Akt pathways (Pernet et

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al., 2007; Zhang et al., 2014b). ODC1 activation by ERK1/2 is also dependent on Ca^{2+}-mediated activation of calpain (Moldoveanu et al., 2002). Interestingly, downregulation of mRNA, protein expression of ERK1/2 and activity of the P42/P44 MAPK complex was reported in the prefrontal cortex (PFC) and hippocampus of MDD-suicide subjects (Dwivedi et al., 2001). Moreover, dual-specificity phosphatase-1 (DUSP1), which is a negative modulator of ERK1/2, was significantly upregulated in CA1 and dentate gyrus (DG) of postmortem MDD subjects (Duric et al., 2010). In animal models acute stress leads to ERK1/2 activation in ventral regions of CA1 and DG, and in the basolateral amygdala (Ritov et al., 2014). In agreement with a role of stress in the activation of ERK1/2, intracerebroventricular injections of the stress hormone corticotropin-releasing hormone (CRH) activates ERK1/2 in principal neurons in CA1 and CA3 of the hippocampus and the lateral and basolateral amygdala (Refojo et al., 2005). Notably, chronic stress leads to hyperphosphorylation of ERK1/2 in distal dendrites of layers II and III of the medialPFC (mPFC) (Trentani et al., 2002), suggesting that activation of ERK1/2 may have localized effects on dendrites and synaptic inputs that alter polyamine biosynthesis metabolism and levels of polyamines locally. Future studies aiming to determine how electrical activity, intracellular [Ca^{2+}] and polyamines are linked through ERK1/2 pathways in neurons is a research priority.

Modulation of neuronal excitability by cytosolic polyamines

Polyamines modulate a broad range of neurotransmitter receptors and ion channels that permeate cations (Table 1). Some polyamine targets drive excitability (e.g. Voltage gated Na^+ and Ca^{2+} channels, ionotropic glutamate and nicotinic receptors) and others maintain resting membrane potential and modulate neuronal firing rate (e.g. inward rectifiers K^+ channels). Therefore, the net effect of polyamine levels on neuronal excitability depends on the particular set, and proportions, of membrane receptors and ion channels in any given region of the brain.

The most well known modulatory effect of cytosolic polyamines on excitability is to limit membrane permeability to cations at depolarized voltages (e.g. voltage-dependent block). For example, polyamines are responsible for the ion current rectification of Ca^{2+}-permeable AMPA receptors (Hume et al., 1991; Pellegrini-Giampietro, 2003; Verdoorn et al., 1991), inward rectifying K^+ channels (Ishihara et al.,

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1996; Kucheryavykh et al., 2007; Lopatin et al., 1994; Yang et al., 1995) and neuronal nicotinic receptors (Haghighi and Cooper, 2000). Polyamines also contribute, along with Mg^{+}, to the rectification of hyperpolarization-activated cyclic nucleotide-gated channels (HCN) (Vemana et al., 2008).

Polyamines normally block AMPA and nicotinic receptors limiting the flow of Na^{+} and Ca^{2+} into the cell during large depolarizations, thereby preventing hyperexcitability and Ca^{2+} overloading. Conversely, a voltage-dependent block of inward rectifying K^{+} currents by polyamines can limit the efflux of K^{+} during the initiation phase of the action potential, thus promoting excitability. In both situations, polyamines determine a temporal- and voltage-dependent window of cation permeability that is optimal for coherent electrical activity and neuronal communication. Polyamines also block Ca^{2+}-permeable AMPA receptors in resting synapses and this block is only removed by fast synaptic activity, whereby high frequency stimulation results in reduction of the polyamine block and potentiation of excitatory synapses. This state-dependent polyamine block of Ca^{2+}- permeable AMPA receptors highlights a role of polyamines in the determination of the timing of synaptic activity (Traynelis et al., 2010).

In general, polyamines have “excitability buffer” properties as they can also negatively modulate the open probability of voltage gated Na^{+} channels (Chen et al., 2007; Fleidervish et al., 2008). Depletion of cytosolic polyamines in layer 5 cortical pyramidal neurons results in increased amounts of openings of Na^{+} channels producing a persistent Na^{+} current and enhanced excitability, leading to spontaneous activity and paroxysmal discharges in these cells (Fleidervish et al., 2008). In contrast, the presence of polyamines reduces the firing of neurons by decreasing the openings of Na^{+} channels (Fleidervish et al., 2008). Thus, when ODC1 is induced by electrical activity, the increased concentration of cytosolic polyamines decreases the amplitude of Na^{+} currents, therefore acting as an important intracellular feedback mechanism to maintain firing rate near a physiological set point.

Modulation of synaptic activity by extracellular polyamines

Polyamines reach the extracellular space by Ca^{2+}-independent and Ca^{2+}-dependent efflux processes (Fage et al., 1993; Fage et al., 1992; Harman and Shaw, 1981). Ca^{2+}-dependent processes can be triggered by depolarization of the membrane via activation

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of NMDA receptors or blockade of Na^+/K^+ transporters (Fage et al., 1993; Fage et al., 1992; Masuko et al., 2003). Additionally, at highly depolarized voltages internal polyamines can permeate through Ca^{2+}-permeable AMPA receptors resulting in the efflux of polyamines to the extracellular space (Traynelis et al., 2010). Thus, overactivation of NMDA receptors or reduced activity of ion pumps by energetic deficiencies may enhance the release of polyamines into the extracellular space where they can positively modulate synaptic receptors like the transient receptor potential cation channel subfamily V member 1 (TRPV1), acid-sensing ion channel 1a (ASIC1a) and some subtypes of NMDA receptors (Table 1).

TRPV1, also known as the capsaicin or vanilloid 1 receptor, is a receptor gated by heat, acidic pH, and endogenous lipids termed “endovanilloids” like unsaturated N-acyldopamines, lipoxygenase products of arachidonic acid and the endocannabinoid anandamide (Van Der Stelt and Di Marzo, 2004). In humans TRPV1 is expressed in hippocampus (Cristino et al., 2006), amygdala (Zschenderlein et al., 2011) and hypothalamus (Cavanaugh et al., 2011), brain regions that participate in the modulation of the stress response. Animal model studies have shown that synaptic TRPV1 activation is critical for long term depression (LTD) in interneurons and participate in long term potentiation (LTP) mechanisms in hippocampal neurons (Brown et al., 2013; Chavez et al., 2010). TRPV1 is sensitized by physiological concentrations of polyamines which lead to a potentiation of responses gated by endogenous agonists (Ahern et al., 2006). At high concentrations, polyamines directly activate TRPV1, with spermine producing the largest response followed by spermidine and putrescine. Because TRPV1 is permeable to polyamines, TRPV1 has also been proposed to be involved in polyamine transport (Ahern et al., 2006). Interestingly, a TRPV1-KO (knockout) mouse model shows less anxiety-related behavior and impaired hippocampus dependent fear memory (Marsch et al., 2007). Because of the TRPV1-KO resilient phenotype, TRPV1 polyamine activation might have a protective effect against anxiety and depression.

Overexpression of the acid-sensing ion channel 1a (ASIC1a) increases amygdala activity and conditioned fear (Wemmie et al., 2004). ASIC1a is involved in the induction of synaptic long term potentiation (Du et al., 2014), is robustly expressed in

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the amygdala, cingulate and nucleus accumbens (Wemmie et al., 2004) and is potentiated by extracellular polyamines (Babini et al., 2002). Conversely, ASIC1a-KO mice show attenuated amygdala activity and, similarly to TRPV1-KO mice, these mice display depressive-resistant behaviors (Coryell et al., 2009; Coryell et al., 2007; Wemmie et al., 2003). Restoration of ASIC1a in the amygdala eliminates the depressive-resistant phenotype of the knockout mice, suggesting a link between ASIC1a expression in the amygdala and depressive behaviors.

NMDA receptors are central in brain function because they participate in synaptic plasticity regulating neuronal communication and modulating behavior (Traynelis et al., 2010). Interestingly, among NMDA receptors, NR2B-containing receptors are the most sensitive to polyamine modulation (reviewed by (Igarashi and Kashiwagi, 2010; Mony et al., 2009; Rock and Macdonald, 1995)). Polyamines enhance ion currents trough NR2B-containing NMDA receptors by glycine-dependent and glycine independent potentiation of ion currents. Polyamines increase the affinity for glycine, an obligated co-agonist of NMDA receptors and reduce proton-mediated tonic inhibition of NMDA receptors at physiological pH (reviewed by (Johnson, 1996)). Interestingly, the binding site for polyamines in NR2B receptors is adjacent to the binding site for NR2B antagonists with antidepressant effects (e.g. ifenprodil).

Role of polyamines in stress response and depression

It is well known in animal models that stress activates both the amygdala and the HPA axis, and triggers the PSR, it is not very clear however how regional increases in activity and the PSR are mechanistically linked. Based on the available evidence, activation of the amygdala-HPA axis during stressful events increases neuronal firing and cytosolic [Ca^{2+}], which, consequently, will produce a fast, neuroprotective increase in ODC1 activity and synthesis of polyamines that would reduce the open probability of Na^{+} channels (Fleidervish et al., 2008). The resulting reduction in Na^{+} currents will lower the electrical firing rate and prevent neuronal hyperexcitability. Thus, the PSR may be part of redundant homeostatic mechanisms aimed to regulate the firing rate and amygdala-HPA axis activity during stressful events.

Because polyamines have important roles in the regulation of gene transcription and post-transcriptional modifications, chronic elevation in polyamine levels, by either

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ODC1 overactivity or deficits in catabolic enzymes like SAT1, can lead to compensatory regulation of membrane proteins involved in excitability, including Na^+ channels. Indeed, the SCN10A gene, which codes for Nav1.8 sodium channels, was differentially expressed in MDD and MDD-suicide postmortem brains (Sequeira et al., 2009). Also, the subunit SCN8A, coding for Nav1.6 and found to be highly expressed in the CNS and the hippocampus (Hawrylycz et al., 2012), has been associated with suicide attempts (Wasserman et al., 2005).

Many gene targets of cytosolic polyamines are also affected in MDD and suicide. GRIA3 downregulation in BA46 of suicide victims without depression as well as in MDD-suicides, and GRIA4 and GRIA2 increased expression in the amygdala and the frontal pole (BA10) in MDD-suicides have been reported using microarrays (Sequeira et al., 2009). Meanwhile, two SNPs (rs4825476 and rs2518224) located within GRIA3 and GRIK2, the latter encoding for a kainate receptor modulated by polyamines, have been significantly associated with treatment-emergent suicidal ideation in MDD (Laje et al., 2007). Similarly, epigenetic studies have found that GRIK2 in MDD and suicide cases is hypomethylated in intron13 suggesting a prevalence of specific splice variants of kainate receptors in MDD and suicide (Nagy et al., 2014).

The CACNA1C gene, coding for the α1c subunit of the Cav1.2 voltage dependent L-type Ca^{2+} channel, has also been associated with mood disorders and MDD (Bhat et al., 2012; Casamassima et al., 2010; Dao et al., 2012; Liu et al., 2011; Shi et al., 2011). L-type Ca^{2+} currents in hippocampus and amygdala are enhanced by corticosteroids through increased synthesis of voltage gated Ca^{2+} channels (Joels and Karst, 2011), and participate in non-NMDA synaptic plasticity events and the formation of fear memory (Bauer et al., 2002). L-type Ca^{2+} channels expressed in neuroblastoma cells are enhanced by cytosolic putrescine, but not spermidine or spermine, via the protein kinase C (PKC) pathway (Herman et al., 1993). During episodes of amygdala excitability, increased activity of ODC1 and higher levels of polyamines will likely increase the consolidation of non-NMDA-dependent fear memory.

Several population based genetic studies have also shown an association between K^+ channels modulated by polyamines and depression. In patients with bipolar disorder for instance, two SNPs (rs2190547 and rs41368245) located near the KCNJ2

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gene, were associated with the number of depressive episodes (Fabbri and Serretti, 2016). The KCNJ2 gene is of interest because it codes for a K^+ channel with strong polyamine-dependent inward rectification (Table 1), and is a gene in which mutations have been implicated in the pathogenesis of Andersen–Tawil syndrome which includes major depression among its clinical symptoms (Chan et al., 2010).

Similarly, a strong association between the rs6686529 SNP, within the KCNK2 gene (potassium channel, subfamily K, member 2; also known as TREK-1), and both MDD and antidepressant response was observed in a clinical cohort. Individuals with homozygous genotypes (CC or GG) for rs6686529 showed greater susceptibility to MDD than those heterozygous for the SNP. Concerning antidepressant response, C-allele carriers demonstrated better remission rates following treatment (Liou et al., 2009). In humans and rodents TREK-1 is highly expressed in the putamen, caudate, amygdala and hippocampus supporting a role in the control of emotion and stress (Hawrylycz et al., 2012; Meadows et al., 2000). The modulation of TREK-1 by polyamines is dependent on the presence of phosphatidylinositol 4,5-bisphosphate (PIP_2) in the membrane. At rest, cytosolic spermine keeps TREK-1 in a closed and inactive state, however, incorporation of PIP_2 into the inner leaflet of the membrane counteracts the polyamine inhibition and renders the channel ready to be activated by stretch, membrane depolarization or H^+ (Chemin et al., 2005). Interestingly, deletion of TREK-1 in mice produces a phenotype that is resistant to induction of depressive behavior, shows enhanced 5-HT transmission in neurons from the hippocampus and dorsal raphe nucleus, and is insensitive to antidepressants typically enhancing 5-HT neurotransmission (e.g. fluoxetine) (Heurteaux et al., 2006). These results strongly suggest that TREK-1 participates in the abnormal hyperexcitability, which characterizes MDD, and might be a potential pharmacological antidepressant target (Heurteaux et al., 2006).

Potassium channels can be modulated by polyamines. The large conductance Ca^{2+}-activated K^+ channels (BK), encoded by the KCNMA1 gene, are also activated by voltage and can regulate neuronal excitability by modifying K^+ permeability depending on the cytosolic Ca^{2+} concentration and voltage depolarizations (Hille, 2001). BK currents participate in the repolarization and after-hyperpolarization of the action

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potential and their blockade by toxins leads to increases in excitability (Gribkoff et al., 2001; Limon et al., 2005). Because BK channels are blocked by cytosolic polyamines (Weiger and Hermann, 1994), an increase in polyamine levels in cells with large expression of BK channels may lead to hyperexcitability. In support of this process, acute and chronic stress has been shown to reduce BK expression in the lateral amygdala of rodents leading to hyperexcitability (Guo et al., 2012; Rosenkranz et al., 2010). Moreover, hyperexcitability in lateral amygdala increased NMDA-mediated excitability of thalamo-amygdalar connections (Rosenkranz et al., 2010), a potential step in the transition to a depressive state. Notably, the rs10740467 SNP near KCNMA1 is one of the most significant markers of comorbidity between MDD and anxiety (Schosser et al., 2013).

Neuronal nicotinic acetylcholine receptors (nAChRs) show polyamine-mediated inward rectification and are blocked by extracellular polyamines (Cooper, 2001). Interestingly, nAChRs have a long and complex history of involvement in stress and MDD. In humans and animal models, blocking the degradation of ACh triggers anxiety and depression (Janowsky et al., 1972; Mineur et al., 2013) and pharmacological antagonism of nAChRs has an antidepressant effect in mice by reducing neuronal activity in the basolateral amygdala. Downregulation of homomeric α7 receptors or heteromeric nAChRs containing the β2 subunit in the amygdala mimics the effects of antidepressants (Mineur et al., 2015). Moreover, depressive symptoms and nicotine dependence are strongly associated across age and duration of lifetime smoking exposure (Dierker et al., 2015). It is still not clear however whether the association between MDD and nicotine-dependence results from one causing the other, or from shared neurobiological circuitry. Association studies found that the rs2072660 SNP in the 3' UTR of the CHRNB2 gene, encoding the β2 nAChR subunit, is associated with suicidal ideation but, has no direct association with MDD unless maternal bonding has been altered (Csala et al., 2015). CHRNB2 has also been shown to have higher levels of methylation in neurons of suicide completers (Labonte et al., 2013).

In addition to nAChRs' role in depression, the antidepressant action of scopolamine, a non-specific muscarinic acetylcholine receptor (mAChR) antagonist, indicates that global alterations of cholinergic neurotransmission are present in MDD

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(Drevets and Furey, 2010; Furey and Drevets, 2006), and because nAChRs and mAChRs have synergic activity on several cognitive functions (Ellis et al., 2006), it is likely that maladaptive interactions between these classes of receptors participate in the maintenance of the depressive status.

Maybe the strongest evidence for the participation of NMDA receptors in MDD came from the fast antidepressant effects of sub-anesthetic doses of ketamine, an antagonist of NMDA receptors with consistent antidepressant and anti-suicidal effects (reviewed by (Reinstatler and Youssef, 2015)). A temporal strengthening of synaptic connectivity in PFC areas seems to be responsible for ketamine effects in MDD, and two principal hypotheses have been proposed to explain the mechanism (Duman et al., 2012; Miller et al., 2016). The first proposes that the direct inhibition of NR2B receptors in cortical, excitatory pyramidal neurons produces a homeostatic upregulation of excitatory drive into these neurons, which leads to enhanced connectivity in PFC areas (Li et al., 2010; Maeng et al., 2008). The other hypothesis proposes that the main target of ketamine are NMDA receptors located at the soma of cortical interneurons which provide inhibitory tone to pyramidal neurons; thus, antagonism of NR2B receptors in interneurons reduces inhibitory drive to principal neurons leading to disinhibition and enhanced connectivity in PFC areas (Miller et al., 2016). Interestingly, both hypotheses require the participation of NR2B receptors, these receptors are highly sensitive to polyamine potentiation. Consistent with a specific role of enhanced NR2B in the pathophysiology of MDD, antagonists of NR2B should produce antidepressant actions similar to ketamine (Maeng et al., 2008; Preskorn et al., 2008).

Although the effects of ketamine and other NR2B-specific antagonists develop fast (sometimes within 20 min (Reinstatler and Youssef, 2015)), they only last for about a week. This temporary effect suggests an increased activity of NR2B in MDD, a possible consequence of a self-sustained maladaptive PSR. In a polyamine-mediated allostatic equilibrium, the pharmacological reduction of NR2B will produce a deviation from the excitability set-point that will be gradually compensated for by other polyamine targets. Therefore, determining whether the expression of NR2B receptors is altered in MDD or if their function is enhanced by abnormal concentrations of polyamines is a research priority.

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Association studies have found SNPs in GRIN2B, the NR2B subunit coding gene, to be associated with MDD. Thus, the rs220549 SNP was found to be associated with neuroticism, a risk factor for MDD in an European cohort (Aragam et al., 2013). Zhang et al., found that the GRIN2B A-G haplotype of the rs1805502 and rs890 SNPs might have a protective role in MDD in a sample of Han Chinese, whereas the G-T haplotype may be a risk factor for the development of treatment-resistant depression (Zhang et al., 2014a). Recent data have found that females with MDD have a higher expression of NMDA receptors in the DLPFC with the expression of GRIN2B also being higher in overall MDD-suicides than in MDD (Gray et al., 2015).

Further studies have highlighted a more specific role of NR2B as a central factor in the pathophysiology of MDD. In animal models NR2B expression is upregulated after stress and its inhibition is sufficient to prevent behavioral deficits induced by stress (Li et al., 2010; Wong et al., 2007). Notably, a mouse model that overexpresses reelin, an extracellular protein involved in neuronal development and glutamatergic neurotransmission (Herz and Chen, 2006), showed less anxiety and was less susceptible to depressive-like behaviors after chronic corticosterone treatment compared to WT mice (Teixeira et al., 2011). This depressive-resistant effect was correlated with a reduction in the expression of NR2B receptors, despite NMDA currents being larger in the reelin-overexpressing mice (Teixeira et al., 2011).

Overall, stress mediated hyperactivity in brain areas involved in depression can result in changes in polyamine metabolism and altered polyamine levels, which can have detrimental effects through modulation of synaptic transmission. A Maladaptive stress response in at risk patients can lead to abnormal polyamine metabolic ratio, due to ODC1 overactivity or SAT1 deficits, this metabolic imbalance can lead to long term increases in polyamines concentrations that saturates their “excitability buffer” capacity and lead to hyperexcitation (Fig. 4).

Conclusions

In this review, we summarize evidence in support of an allostatic model of depression. According to this model, chronic elevations of polyamine levels result in a self-sustained stress response which is maintained by maladaptive homeostatic mechanisms (Fig. 4).

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Specifically, in vulnerable individuals exposure to chronic or acute stress can lead to hyperexcitabity of the amygdala, which will induce a persistent elevation of ODC1 gene expression leading to subsequent increases in polyamine levels.

Under normal conditions a transient induction of cytosolic polyamines occurs and excitability is buffered through modulation of Na^+, K^+ and Ca^{2+} channels, as discussed above. However, in depression this increase in polyamine levels does not return to baseline, due to an excess of polyamine anabolism, deficits in polyamine catabolism, and alterations of polyamine targets, and a feed-positive mechanism of excitability is set in motion. Chronic stress and high amygdala activity will maintain high levels of cytosolic polyamines potentiating L-type Ca^{2+} channels and blocking K^+ and Ca^{2+}-activated K^+ channels, promoting excitability. The resultant high levels of electrical and neuronal activity may lead to energetic deficits that, together with high concentrations of cytosolic polyamines, would incrementally increase polyamine efflux to the extracellular space where they positively modulate ASIC1, TRPV1, and NR2B and further promote excitability. Under these conditions PFC circuits and compensatory mechanisms cannot modulate amygdala hyperexcitability. Therefore, changes in intrinsic properties and remodeling of neuronal connectivity are put in place until a novel allostatic equilibrium within frontocortical-limbic structures, with higher amygdala activity is established. A better understanding of the role of polyamines during the transition from health to MDD and the compensatory changes occurring in neuronal activity, within the context of excitability, may identify novel nodes of homeostatic control that could be susceptible to therapeutic manipulation.

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Figure Captions

Figure 1. Chemical structure of positively charged polyamines in solution.

Figure 2. Polyamine metabolism and potential induction pathways in neurons. Membrane proteins that permeate Ca^{2+} during cellular activity induce ODC activity and increases cytosolic polyamine concentration. Although It is not known if Ca^{2+} can directly induce ODC activity there are two alternative pathways that are known to induce ODC activity in cardiac cells. The activity of ODC is negatively regulated by antizyme and the concentration of polyamines are controlled by anabolic (green boxes) and catabolic (red boxes) enzymes. NMDAR, NMDA-type glutamate receptor; nAChR, nicotinic acetylcholine receptor; AMPAR, AMPA-type glutamate receptor; VGCC, voltage-gated Ca^{2+} channels; P42/P44 MAPK, P42/P44 mitogen-activated protein kinase signaling; P13K/AKt, phosphoinositide 3-kinase/Protein kinase B signaling; ODC, L-ornithine decarboxylase; AMD1, S-adenosylmethionine decarboxylase; SRM, Spermidine synthase; SMS spermine synthase; SMO, spermine oxidase; SAT1, spermidine/spermine-N1-acetyltransferase; PAOX, acetylpolyamine oxidase.

Figure 3. Polyamine system interdependence with fundamental properties of neuronal electrical activity. Each box indicates the membrane protein targets (in bold) that are modulated by cytosolic or extracellular polyamines. More information about the specific type of modulation is found in table 1.

Figure 4. Polyamine dysregulation in MDD. In health a balanced polyamine metabolism (represented by the ratio ODC1/SAT1 = 1) will provide a concentration of polyamines required for the normal modulation of cationic receptors and channels. Abnormal polyamine metabolic ratio, due to ODC1 overactivity or SAT1 deficits, may produce a long term increase in polyamines concentrations that saturates its “excitability buffer” capacity and lead to hyperexcitation. Excess of polyamines may increase the efflux of polyamine and potentiate excitatory synapses through sensitization of NMDAB, ASIC1a, nicotinic and TRPV receptors that are highly expressed in brain regions involved in emotion and stress control, and are positively modulated by polyamines.

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Long term stress-driven and polyamine-enabled excitation may lead to remodeling of neuronal properties that underlies the hyperexcitability and hyper-reactivity found in MDD.

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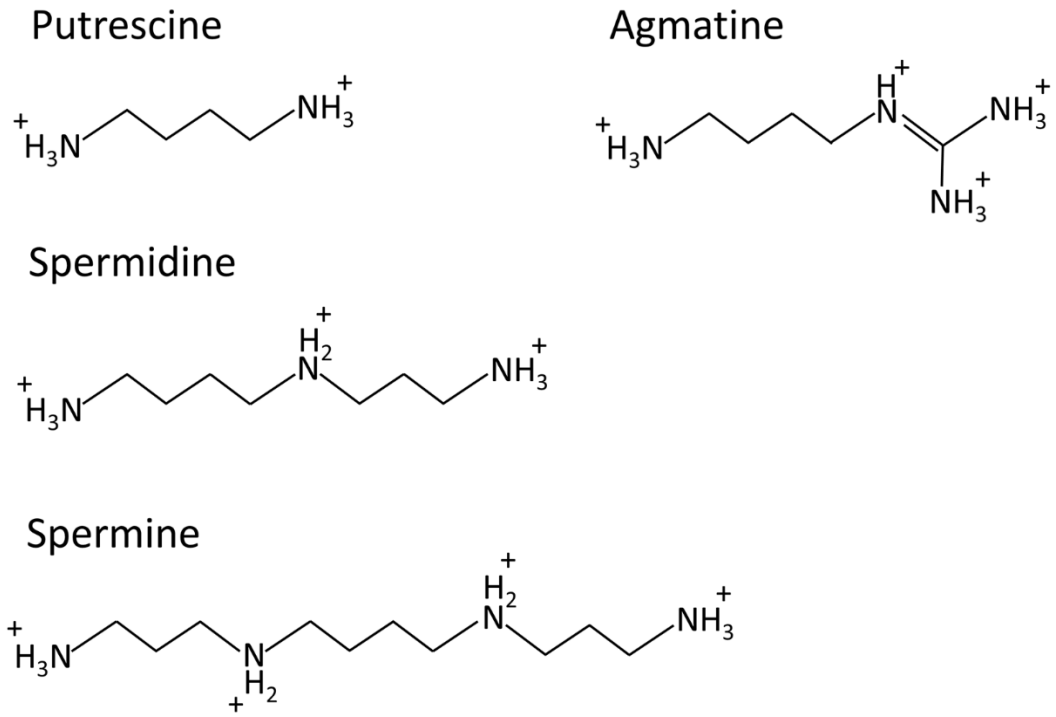


Figure 1

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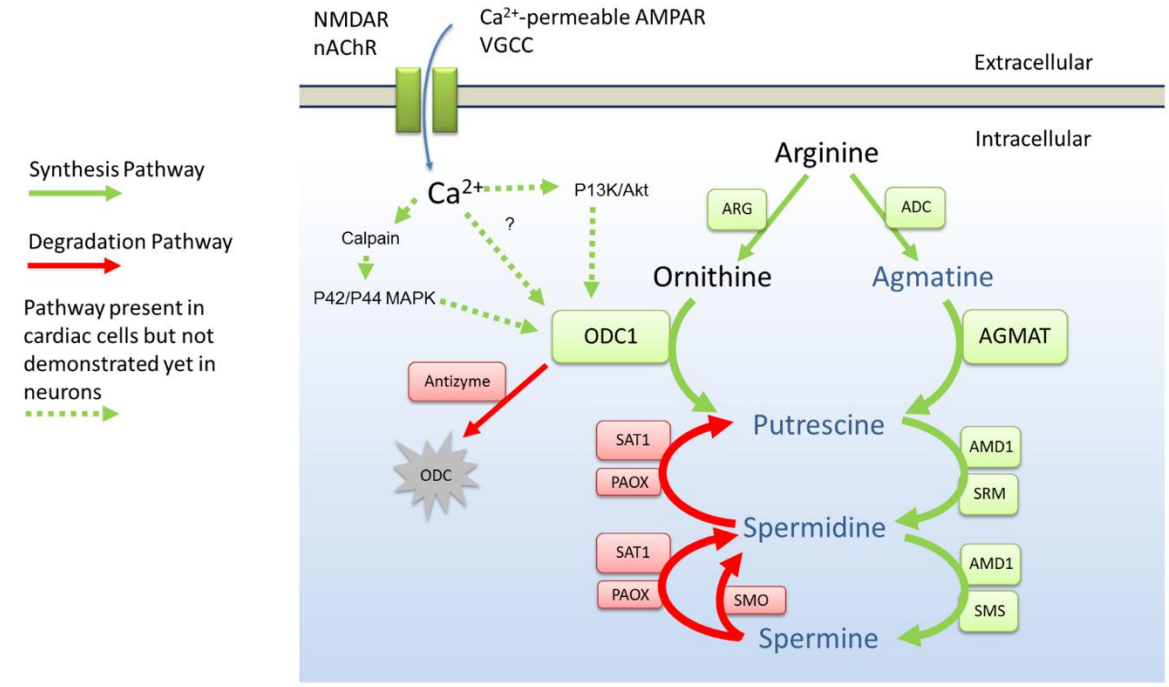


Figure 2

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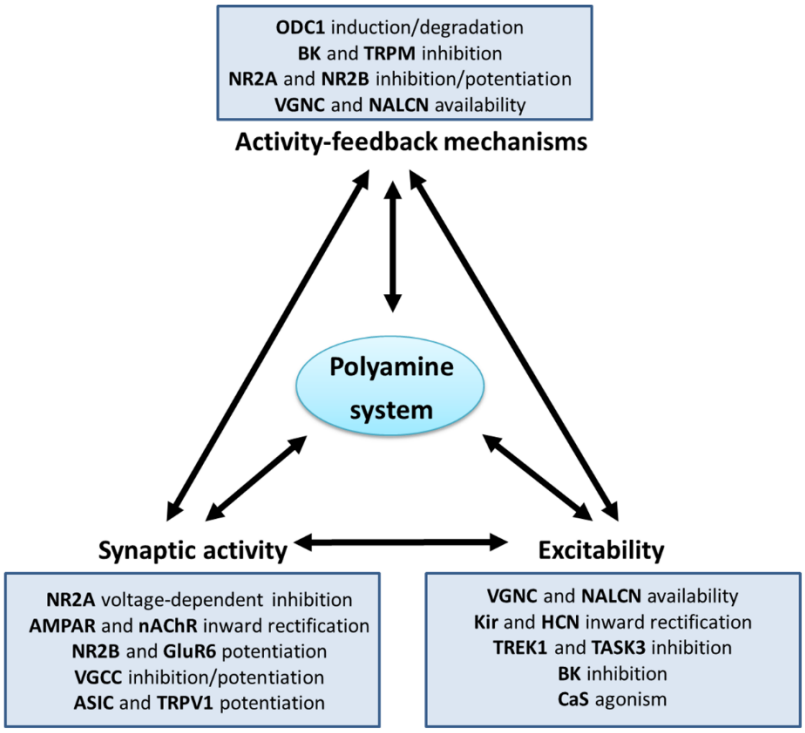


Figure 3

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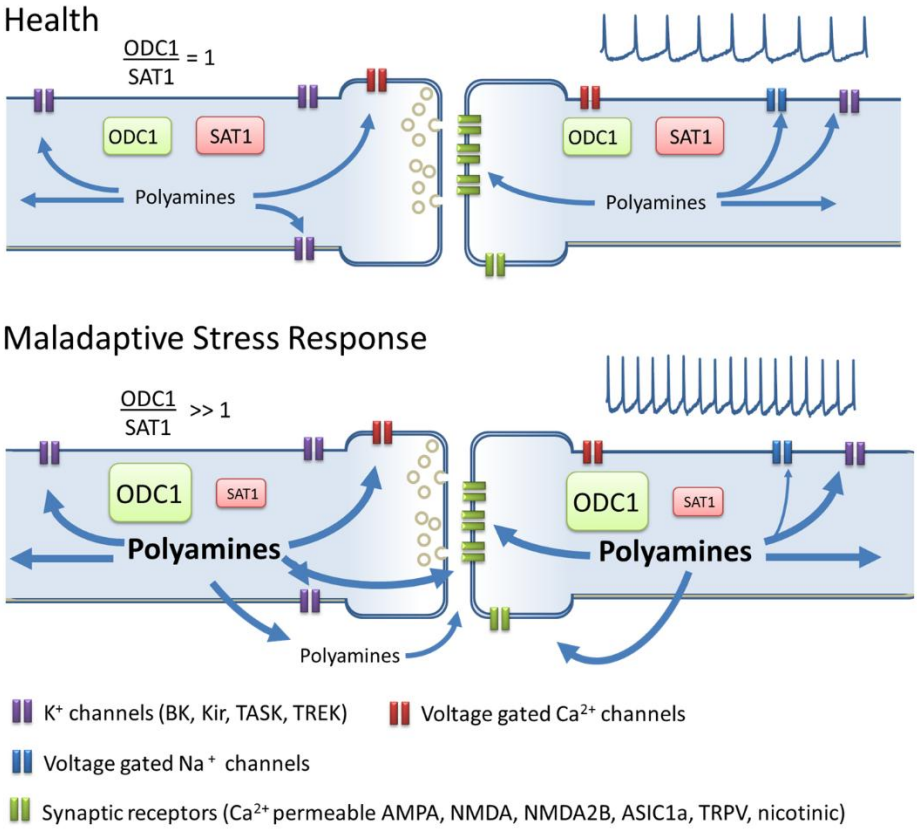


Figure 4

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Tables

Table 1. Membrane targets of polyamine modulation involved in control of electrical activity

Category	*Gene*	*Protein*	*Action*	*Function of protein*
NMDA receptors	GRIN1	NR1A	↓ Voltage dependent inhibition (NR1A-NR2A) (Gallagher et al., 1997; Traynelis et al., 1995; Williams et al., 1995; Williams et al., 1994; Zhang et al., 1994) ↑ Glycine-dependent stimulation (NR1A-NR2B)	Glutamate receptor, synaptic component, Ca^{2+} permeability, Involved in LTD, LTP and excitotoxicity
	GRIN2A	NR2A		
	GRIN2B	NR2B	↑ Glycine independent-stimulation (NR1A-NR2B) ↑ Glycine-dependent stimulation (NR1A-NR2B) ↓ Decrease affinity for agonists (NR1A-NR2B) ↓ Voltage dependent inhibition (NR1A-NR2B)	
AMPA receptors	GRIA1	GluR1	↓ Voltage dependent blocking (inward rectification) (Hume et al., 1991; Verdoorn et al., 1991)	Glutamate receptor, synaptic component, involved in induction of LTP, Ca^{2+} permeability
	GRIA2	GLuR2(Q)		
	GRIA3	GLuR3		
	GRIA4	GLuR4		
Kainate receptors	GRIK2	GluR6(Q)	↓ Inhibition by spermine and spermidine (Mott et al., 2003)	Glutamate receptor, Synaptic component.
		GLuR6(R)	↑ Potentiation by relieving proton inhibition of the receptor	
Ach nicotinic receptors	CHRNA7	$\alpha 7$	↓ Voltage dependent blocking (inward rectification)(Charnet et al., 1992; Gerzanich et al., 1994)	Presynaptic and postsynaptic receptor. Modulates release of 5-HT, Dopamine and noradrenaline
	CHRNA4	$\alpha 4\beta 2$	↓ open pore blocker(Haghighi and Cooper, 1998)	
	CHRNB2	$\alpha 4\beta 2$		
K^+ channels	KCNJ1	Kir1.1	↓ Voltage dependent blocking (mild inward rectification) (Ishihara et al., 1996;	Voltage dependent K^+ channels, modeling of action

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			Kucheryavykh et al., 2007; Lopatin et al., 1994; Murrough et al., 2013; Yang et al., 1995)	potentials, membrane potential.
	KCNJ2	Kir2.1		
	KCNJ3	Kir3.1	↓ Voltage dependent blocking (strong inward rectification)	
	KCNJ4	Kir2.3		
	KCNJ5	Kir3.4	↓ Voltage dependent blocking. Intermediate sensitivity	
	KCNJ10	Kir1.2	↓ Fast blocking and posterior permeation	
	KCNQ2	Kv7.2	↓ Inhibition, indirectly by binding to intracellular PIP_2 (Suh and Hille, 2007) (Chemin et al., 2005)	Voltage dependent K^+ channel. Inhibited by muscarine
	KCNQ3	Kv7.3		
	KCNK2	TREK-1	↓ Inhibition by intracellular spermine	Control of resting membrane potential
	KCNK9	TASK-3	↓ Blocking by extracellular spermine (Musset et al., 2006)	
H^+ receptors	ASIC1	ASIC1	↑ Spermine-mediated sensitization of ASIC1a (Babini et al., 2002; Li et al., 2010)	Cationic permeability,
Na^+ channels	?	Nav ?	↓ Activity dependent inhibition (Chen et al., 2007; Fleidervish et al., 2008)	Initiation and maintenance of action potentials
Ca^{2+} channels	CACNA1B	Cav 2.2 (N-type)	↓ Inhibition, shift in activation and decreased permeability (Chen et al., 2007; Cino and Formenti, 2008; Herman et al., 1993; Lasater and Solessio, 2002; Weiger and Hermann, 1994)	Synaptic vesicular release, Ca^{2+} permeability
	CACNA1C	Cav 1.2 (L-type)	↑ PKC-mediated potentiation (Putrescine)(Herman et al., 1993)	Ca^{2+} permeability, NMDA-independent LTP
Ca^{2+} activated K^+ channels	KCNMA1	BK, KCa1.1	↓ Blocking and reduction of open probability(Weiger and Hermann, 1994; Weiger et al., 1998)	K^+ permeability dependent on voltage and Ca^{2+} convergence
Ca^{2+} activated cationic channel	TRPM4	TRPM4	↓ Channel blocker, (Antagonist) (Nilius et al., 2004; Ullrich et al., 2005)	Ca^{2+} permeability, Ca^{2+} sensor, intracellular ATP binding
	TRPM5	TRPM5		
	TRPM7	TRPM7	↓ Channel blocker, (inhibition) (Kerschbaum et al., 2003)	

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Capsaicin receptor	TRPV1	TRPV1	↑ Agonist (Ahern et al., 2006)	Cationic permeability, involved in LTD
Extracellular Ca^{2+} sensor	CASR	CaS receptor	↑ Agonist (Hofer and Brown, 2003; Quinn et al., 1997)	Membrane Ca^{2+}-sensing GPCR
Na^{+} leak channel	NALCN	NALCN	↓ when coupled to Cas Receptor spermine inhibits the channel (Lu et al., 2010)	Resting membrane potential and excitability
Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels	HCN1 HCN2 HCN3 HCN4	HCN1 HCN2 HCN3 HCN4	↓ Voltage dependent blocking (inward rectification)(Vemana et al., 2008)	Resting membrane, excitability.
Intracellular enzymes	PLCD1	PLCδ1	↑ Endogenous activator (spermine) (Haber et al., 1991)	Membrane Phospholipase
Transporter	SLC12A8	CCC9	Spermine and spermidine are substrates (Daigle et al., 2009)	$Na^{+}/K^{+}/Cl^{-}$ membrane transporter
GABA receptor	?	?	Modulation of diazepam and flunitrazepam binding(Gilad et al., 1992a)	Inhibitory receptor

Abbreviations: LTP, long term potentiation; LTD, long term depression; GPCR, G-protein coupled receptor.