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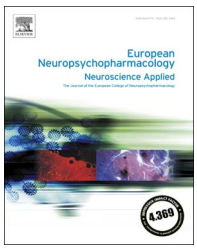

REVIEW

A novel mechanism of depression: role for connexins

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Abstract
Major depressive disorder (MDD) is a chronic and debilitating illness that affects over 350 million people worldwide; however, current treatments have failed to cure or prevent the progress of depression. Increasing evidence suggests a crucial role for connexins in MDD. In this review, we have summarised recent accomplishments regarding the role of connexins, gap junctions, and hemichannels in the aetiology of MDD, and discussed the limitations of current research. A blockage of gap junctions or hemichannels induces depressive behaviour. Possible underlying mechanisms include the regulation of neurosecretory functions and synaptic activity by gap junctions and hemichannels. Gap junctions are functionally inhibited under stress conditions. Conversely, hemichannel permeability is increased. Antidepressants inhibit hemichannel permeability; however, they have contrasting effects on the function of gap junctions under normal conditions and can protect them against stress. In conclusion, the blockage of hemichannels concurrent with improvements in gap junction functionality might be potential targets for depression treatment.

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1. Introduction

Major depressive disorder (MDD) is psychiatric syndrome that affects over 350 million people worldwide (Smith, 2014) and will rank as the second-leading cause of death and disability by 2020 (Gerhard et al., 2016; Saavedra et al., 2016). Moreover, MDD exacts a very large economic burden that is 10.3% of the total burden of disease (Smith, 2014), but currently, there is no effective treatment (Alberich et al., 2016). Monoamines, such as serotonin, norepinephrine, and dopamine; glutamate receptors; epigenetic modifications; hypothalamic-pituitary-adrenal (HPA) axis; inflammatory cytokines; and neurotrophic factors are associated with the neuropathology of MDD (Cai et al., 2015; Czeh et al., 2016). Monoamine neurotransmitter imbalance is the most widely accepted hypothesis for the aetiology of MDD. Subsequently, a series of antidepressants were developed, such as serotonin (5-HT) selective reuptake inhibitors (SSRIs); however, they have a significant lag time to treatment response (Chopra et al., 2011). Increasing evidence indicates that ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist, has a rapid antidepressant action. Consequently, research has shifted to glutamate and gamma-aminobutyric acid (GABA) systems (Costi et al., 2015). The release of these gliotransmitters is closely related to the function of connexins (Montero and Orellana, 2015); however, the research and application of ketamine has been restricted by its illicit nature and potentially adverse side effects (Costi et al., 2015).

Recent reports suggest that gap junction dysfunction can induce depressive behaviour (Sun et al., 2012). The gap junction is formed by interactions between the extracellular loops of two hemichannels in the plasma membrane and regulates the communication of ions between adjacent cells, such as Ca^{2+}, Na^{+}, and K^{+}; second messengers, such as IP_3, cAMP, and cGMP; metabolites, such as glutamate, glucose, and glutathione; and other small molecules <1.5 kDa (Goldberg et al., 1999; Harris, 2007; Orellana et al., 2013). Six connexins oligomerise into one hemichannel that is generally closed before docking with another hemichannel (Bennett et al., 2003). Uncoupled hemichannels function in membranes, in addition to forming gap junctions, by regulating the uptake and release of small molecules between the cytoplasm and the extracellular space (Orellana et al., 2013). Connexins have been translated into therapeutics due to their key role in regulating cell-to-cell communication, such as improving healing of epithelial tissue, reducing scar tissue deposition, and preventing vascular die-back (Becker et al., 2016). In addition, connexins are thought to play an important role in central neural system (CNS) disease, including epilepsy, stroke, and neurodegenerative diseases (Nemani and Binder, 2005; Schulz et al., 2015; Takeuchi and Suzumura, 2014). Inhibition of Cx43 gap junction channels by Gap27 diminishes spontaneous seizures (Mylvaganam et al., 2014). Similarly, inhibition of Cx43 by Gap26 and Gap27 reduces cerebral infract volume, improving functional recovery in neonatal rats after hypoxia/ischemia (Li et al., 2015). In this review, we discuss the current opinion about the role of connexins in depression.

2. Function of connexins

Almost all the cell types express connexins in the brain. Cx30.2, Cx31.1, Cx32, Cx36, Cx50, and Cx57 are mainly expressed in neurons; however, Cx32 and Cx36 are also expressed in microglia (Decrock et al., 2015; Willebrords et al., 2017a). Cx26, Cx30, and Cx43 are mainly expressed in astrocytes, with Cx43 also expressed in activated microglia (Eugenin et al., 2001; Martinez et al., 2002; Sun et al., 2005; Willebrords et al., 2017a). Cx40 and Cx45 are expressed in both neurons and astrocytes (Decrock et al., 2015; Willebrords et al., 2017a). Connexins form homocellular, such as neuron-neuron and astrocyte-astrocyte, and heterocellular, such as neuron-astrocyte, gap junctions (Nagy and Rash, 2000). The opening and closing of gap junctions and hemichannels is regulated by connexins phosphorylation, which is summarised in Table 1. Connexins perform different functions dependant on cell type and structure. These functions are discussed in the following sections.

2.1. Gap junctions

2.1.1. Astrocytes

Connexins have been shown to regulate synaptic activity in astrocytes *via* gap junction-mediated neuron-glia interactions (Chever et al., 2014b; Rouach et al., 2004). Astrocytes deliver energetic metabolites to neurons *via* gap junctions formed of Cx43 and Cx30 (Rouach et al., 2008). Cx30 controls hippocampal excitatory synaptic transmission through the modulation of astroglial glutamate transport (Pannasch et al., 2014). Excitatory synaptic transmission in Cx30 $^{-}/^{-}$ mice decreases as a result of reduced synaptic glutamate; however, the surface α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor density and AMPA/ N-methly-d-aspartate (NMDA) ration are unchanged (Pannasch et al., 2014). In addition, the glutamatergic synaptic activity of hippocampal CA1 pyramidal cells can be modulated by Cx43 (Chever et al., 2014b).

Gap junctions in astrocytes are associated with the extent of intercellular calcium wave propagation (Blomstrand et al., 1999); and serotonergic and glutamatergic signalling pathways (Schipke et al., 2011). Moreover, the calcium wave has recently been identified as a potent modulator of synaptic transmission (Jedrzejewska-Szmek et al., 2016). Heteromeric gap junctions exhibit faster intercellular Ca^{2+} signalling than their homomeric counterparts (Cotrina et al., 2000; Sun et al., 2005). ATP and IP_3 passed thorough gap junctions regulated the communication of Ca^{2+} signals (D'Hondt et al., 2007; Lock et al., 2016; Scemes and Giaume, 2006). Connexins in astrocytes also modulate the plasticity of glioma stem-like cells (GSCs); Cx43 is overexpressed in GSCs non-stem-like states, whereas Cx46 is overexpressed in GSCs stem-like states (Balca-Silva et al., 2017). Ablation of Cx43 in astrocytes significantly diminishes neural proliferation and survival, whereas ablation of Cx30 shows the opposite tendency (Liebmann et al., 2013). Cx43 knockout astrocytes induce the loss of long-lasting plasticity in the mouse

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