Neuroscience and Biobehavioral Reviews 77 (2017) 317–326

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Serotonin and neuroplasticity – Links between molecular, functional and structural pathophysiology in depression

Christoph Kraus[a], Eero Castrén[b], Siegfried Kasper[c], Rupert Lanzenberger[a,*]

[a] NEUROIMAGING LABs (NIL) – PET & MRI & EEG & Chemical Lab Department of Psychiatry and Psychotherapy Medical University of Vienna
[b] Neuroscience Center, University of Helsinki, Helsinki, Finland
[c] Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria[1]

ARTICLE INFO

Article history:
Received 15 January 2017
Received in revised form 23 February 2017
Accepted 12 March 2017
Available online 22 March 2017

Keywords:
Neuroplasticity
Serotonin
Depression
Neurogenesis
Structural magnetic resonance imaging
Voxel-based morphometry
Brain-derived neurotrophic factor

ABSTRACT

Serotonin modulates neuroplasticity, especially during early life, and dysfunctions in both systems likewise contribute to pathophysiology of depression. Recent findings demonstrate that serotonin reuptake inhibitors trigger reactivation of juvenile-like neuroplasticity. How these findings translate to clinical antidepressant treatment in major depressive disorder remains unclear. With this review, we link preclinical with clinical work on serotonin and neuroplasticity to bring two pathophysiologic models in clinical depression closer together. Dysfunctional developmental plasticity impacts on later-life cognitive and emotional functions, changes of synaptic serotonin levels and receptor levels are coupled with altered synaptic plasticity and neurogenesis. Structural magnetic resonance imaging in patients reveals disease-state-specific reductions of gray matter, a marker of neuroplasticity, and reversibility upon selective serotonin reuptake inhibitor treatment. Translational evidence from magnetic resonance imaging in animals support that reduced densities and sizes of neurons and reduced hippocampal volumes in depressive patients could be attributable to changes of serotonergic neuroplasticity. Since ketamine, physical exercise or learning enhance neuroplasticity, combinatory paradigms with selective serotonin reuptake inhibitors could enhance clinical treatment of depression.

Contents

1. Introduction

Serotonin is an important neuromodulatory transmitter with distinctive neuroplastic capabilities. While synaptic plasticity is a well-known key mechanism in learning and memory (Dayan and Cohen, 2011; Kandel, 2001), unequivocal studies suggest that dysfunction of synaptic plasticity with neuronal atrophy and cell death contribute to the pathophysiology of depression and therapeutic response could be associated with overcoming this deficit (Duman

* Corresponding author at: NEUROIMAGING LABs (NIL) – PET & MRI & EEG & Chemical Lab, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Wien, Austria.
E-mail address: rupert.lanzenberger@meduniwien.ac.at (R. Lanzenberger).
[1] http://www.meduniwien.ac.at/neuroimaging/.

http://dx.doi.org/10.1016/j.neubiorev.2017.03.007
0149-7634/

and Aghajanian, 2012; Krystal et al., 2013; Shakesby et al., 2002). This suggests that problems of information processing within neuronal networks associated with neuromorphological changes underlie depression (Castrén, 2005).

Clear-cut data demonstrate that 5-HT shapes neuronal networks during development and deficiencies thereby fundamentally impact the pathophysiology and long-term outcome of brain disorders (Lesch and Waider, 2012). Beyond their known neurochemical mechanisms of action, selective 5-HT reuptake inhibitors (SSRIs) might reactivate serotonin's ability to mediate developmental plasticity (Castren and Rantamaki, 2010; Vetencourt et al., 2008). Close molecular connections between serotonergic receptors and neurotrophic proteins as brain-derived neurotrophic factor (BDNF) and intracellular signaling cascades are responsible for cytoskeletal rearrangement (Mattson et al., 2004; Rantamaki and Castren, 2008); see Table 1). Serotonin modulates glutamatergic transmission and might kindle N-methyl-D-aspartate (NMDA) receptor dependent plasticity (Bennett, 2010; Sanacora et al., 2012). Moreover, 5-HT is linked to cell adhesion molecules (Lesch and Waider, 2012), which are part of the extracellular matrix and crucial for developmental plasticity (Varea et al., 2007). Environmental effects might be a crucial modulating factor for serotonergic neuroplasticity, whereby stress and negative events were demonstrated to be functionally relevant to SSRI-mediated neuroplasticity in animal models (Alboni et al., 2017; Wu et al., 2014). Hence, data suggesting that SSRIs might reactivate developmental plasticity are sound, yet these results were made in animals and translational evidence in humans is missing.

Consistent with the neuroplasticity deficits, an increasing number of neuroimaging studies identified alterations of neuroplasticity with magnetic resonance imaging (MRI; Zatorre et al., 2012). Reductions in gray matter volume (GMV) were observed in cross-sectional studies in patients with depression (van Tol et al., 2010) and corroborated by meta-analyses (Kempton et al., 2011; Wise et al., 2016). Interestingly, SSRIs were demonstrated to increase hippocampal (Arnone et al., 2013) and other limbic GMV (Hoexter et al., 2012; see Table 2). Novel rapidly acting antidepressants in the glutamate system such as ketamine are thought to exert at least parts of their action by stimulating neuroplasticity (Krystal et al., 2013). Moreover, structural changes were demonstrated in healthy subjects with longitudinal designs in learning paradigms, associated with experience of navigation or musical training to name only a few (Draganski et al., 2006; Hyde et al., 2009; Maguire et al., 2000).

This suggests that the adult brain is able to structurally adapt to internal or external stimuli and 5-HT might play an important role. In this review we aim to summarize the current knowledge of serotonin-mediated neuroplasticity, its assumed role in depression and treatment with serotonergic antidepressants. Moreover, we discuss how neuroplasticity can be measured *in vivo* in humans and how preclinical work on serotonergic neuroplasticity could be translated to patient studies.

2. Mechanisms of neuroplasticity and their importance in the pathophysiology of depression

Neuroplasticity is an umbrella term for the brain's ability to structurally adapt to changes of the internal or external milieu (May, 2011; Pascual-Leone et al., 2005). As a specific form of neuroplasticity, synaptic plasticity refers to one of the most crucial functions of the brain – it is the ability to sense, assess and store information and to modify synaptic transmission according to subsequent stimuli (Citri and Malenka, 2008; Duman et al., 2016). Thereby regulation of synaptic numbers is often referred to as synaptogenesis or synaptic homoeostasis, which are crucial during neuronal development in early life. Neurogenesis is the term for newly born neurons (Eriksson et al., 1998). According to current knowledge in adulthood neurogenesis is restricted to the hippocampus, rudimentarily present in the olfactory bulb and possibly occurring in the striatum (Bergmann et al., 2015; Ernst et al., 2014).

2.1. Plasticity during neuronal development

Serotonin mediates autoregulatory effects in growing serotonergic neurons (Whitaker-Azmitia, 1998), catalyzes the maturation of astroglial cells (Whitaker-Azmitia, 1998) and influences target tissue maturation (Whitaker-Azmitia et al., 1996). Transgenic mice entirely lacking serotonergic neurons exhibit high perinatal mortality rates and severe deficits in respiratory control (Hodges et al., 2009). Reversible inhibition of 5-HT synthesis by blocking the brain isoform of the tryptophan hydroxylase (Tph2) during early embryogenesis with DL-P-chlorophenylalanine (PCPA) results in subtle alterations of neuronal populations as well in reduced dendritic arborization and complexity, which was independent of neurotrophin signaling (Vitalis et al., 2007).

Irreversible loss of 5-HT after replacing Tph2 with an enhanced green fluorescent protein resulted in reduced serotonergic innervation in thalamic and hypothalamic nuclei, and increased serotonergic nerves in nucleus accumbens (Migliarini et al., 2013). Most strikingly, macroscopic brain development is unaffected, while mice exhibit high lethality rates and body growth reduction. Moreover, in the hippocampus of Tph2 knockout mice BDNF was upregulated indicating presence of compensatory mechanisms. These subtle changes of serotonergic innervation upon Tph2 knockout were not detected in earlier immunohistochemistry studies *e.g.*: (Gutknecht et al., 2008). Moreover, expression of serotonergic receptor mRNA upon lack of 5-HT due to Tph2 knockout was found to be unchanged (Kriegebaum et al., 2010), which the authors trace back to preserved genetic programs independent of 5-HT itself.

Excess 5-HT produces dystrophic serotonergic neurons (Daubert et al., 2010) and migration defects in retinal projection neurons (Upton et al., 1999), thalamocortical axons (Vitalis et al., 2002) and cortical interneurons (Riccio et al., 2009). While many of the neurobiological mechanisms in control of neuroplastic changes during the brain's development seem to reduce their potency in adulthood resulting in a lower threshold for plasticity, SSRIs could lower this threshold by reactivation of developmental plasticity.

Malfunction of developmental plasticity may lead to cortical malfunctions and dystrophic serotonergic neurons as observed in neurodevelopmental disorders (Gaspar et al., 2003; Lesch and Waider, 2012; Whitaker-Azmitia, 2001). Until very recently, the impact of deficits in 5-HT-mediated neuronal development on adult emotional and cognitive function was hardly known. But, accumulating animal data demonstrate developmental periods sensitive to serotonergic and dopaminergic signaling affect later-life somatosensory, anxiety/depression-like and aggressive behavior (Suri et al., 2015). While early-life stress poses a risk factor for depression by altering hypothalamic–pituitary–adrenal (HPA) axis or hippocampus function (Frodl and O'Keane, 2013), entangling protective or aversive genetic and environmental conditions during these critical periods might pose a lucrative field of innovative investigations.

2.2. Synaptic plasticity

Cellular mechanisms controlling synaptic plasticity are thought to represent the biological correlate of learning and memory in the brain (Kandel, 2001), and can be divided into large-scale adaptations like axonal or dendritic sprouting or pruning, and smaller