Biochemical Pharmacology 141 (2017) 86–99

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Review

Adult hippocampal neurogenesis: Is it the alpha and omega of antidepressant action?

Hoda Eliwa, Catherine Belzung *,[1], Alexandre Surget [1]

U930 Imaging and Brain, Inserm & Université François Rabelais, Tours, France

ARTICLE INFO

Article history:
Received 30 April 2017
Accepted 4 August 2017
Available online 8 August 2017

Keywords:
Antidepressants
Neurogenesis
Hippocampus
Neurostimulation

ABSTRACT

It is now well established that all clinically available antidepressants share a common aptitude: they increase the production of adult-generated neurons in the dentate gyrus of the hippocampus. This was first observed in animal models and subsequently in human populations, highlighting the clinical relevance of this finding. Later, it was suggested that hippocampal neurogenesis was not an epiphenomenal correlate of antidepressant action but was causally involved. Indeed, when neurogenesis is suppressed, antidepressant compounds can no longer achieve remission. This action of adult-born neurons seems necessary to achieve remission, but less evidence exists to show that it is sufficient alone. In the following decades, a new generation of putative antidepressants that act through different non-monoaminergic mechanisms were proposed in preclinical research as potential therapies. Interestingly, these treatments all increased neurogenesis in animal models of pathological states: this was observed with drugs acting through peptidergic or glutamatergic mechanisms and with neurostimulation strategies not targeting the hippocampus. However, the involvement of neurogenesis was not always causal. To advance further in this field, an understanding of how adult-generated neurons induce therapeutic effects and how this is related to the pathophysiology of depression are required.

Contents

* Corresponding author at: Inserm 930, Université François Rabelais, UFR Sciences et Techniques, Parc Grandmont, F-37200 Tours, France.
E-mail address: catherine.belzung@univ-tours.fr (C. Belzung).
[1] Both authors contributed equally to the present work.

http://dx.doi.org/10.1016/j.bcp.2017.08.005
0006-2952/

1. Introduction

Stress-related disorders such as major depression or post-traumatic stress disorders have a huge impact on public health in modern industrial societies. For example, major depressive disorders are one of the main contributors to the global burden of disease [1], with a lifelong prevalence of around 16.2% [2], while post-traumatic stress disorders have a lifelong prevalence estimated at around 8.3% of the United States population [3]. Both pathologies are generally treated initially using a chronic administration of molecules termed as antidepressants (ADs), although their therapeutic effects may not completely coincide with their aptitude to reverse depression. Indeed, (a) the term 'antidepressant' seems inaccurate as these drugs are used to treat diseases other than depression (such as panic or post-traumatic stress disorders), and moreover, (b) not all depressed patients respond to the treatment. For example, according to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only 28% of the depressed patients achieved remission after a first-line treatment with these molecules [4]. Nonetheless, ADs have become the third most prescribed medication in the United States [5].

2. Monoaminergic AD drugs

Several chemical classes of ADs are currently available commercially, including selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (NRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclics (TCAs) and monoamine oxidase inhibitors (MAOIs). The therapeutic actions of the MAOI iproniazid and of the TCA imipramine were discovered by serendipity in 1957. These medications were pivotal in AD research. At that time, it should be noted that Kuhn, for example, only used his subjective feeling to establish the efficacy of the treatment and did not employ more objective measures such as standardized rating scales for depression. Regarding MAOI iproniazid, it was administered to patients with tuberculosis and was found to elicit euphoria and was then marketed in 1958. The year before, Brodie et al. [6] discovered the target underlying the effects of iproniazid, i.e. that the drug induced an increase in both serotonin and norepinephrine by inhibiting monoamine oxidase (MAO), an enzyme catalyzing the oxidation of monoamines such as norepinephrine (also called noradrenaline) and serotonin. Interestingly, the TCA imipramine also elicits an increase in serotonin and norepinephrine, although the underlying molecular mechanisms differ, with the effects of imipramine occurring through inhibition of serotonin and norepinephrine transporters and not through the inhibition of MAOs [7].

The mechanisms by which these two compounds, often referred to as first-generation ADs, act provided a template for developing newer classes of ADs 20 years later. These latter second-generation ADs aimed to target more specifically the serotoninergic or noradrenergic systems. For example, SSRIs specifically stimulate serotoninergic neurotransmission by increasing the availability of synaptic serotonin as they block its natural reuptake. In the mid-1970s, Fuller, Wong, Molloy and colleagues published the first reports on the effects of SSRIs [8–11], showing that fluoxetine, a molecule from this class, had a highly potent effect on serotonin reuptake. During the 1980s, many other SSRIs (citalopram, paroxetine, etc.) received marketing authorization for the treatment of depression. Another approach consisted in focussing exclusively on the noradrenergic component using NRIs such as reboxetine; these molecules block the norepinephrine transporter, which in turn leads to increased extracellular levels of norepinephrine in the synaptic cleft.

In recent years, few new ADs have become available, with the exception of dual SNRIs, vilazodone and agomelatine. The American Food and Drug Administration (FDA) approved SNRIs such as venlafaxine, duloxetine and milnacipran in 1993, 2004 and 2009, respectively. These molecules act on serotoninergic and noradrenergic mechanisms, as is the case with first- and second-generation ADs, but their spectrum of action is broader. For example, venlafaxine acts on dopamine in addition to noradrenaline and serotonin, and the onset of its action is more rapid. The effects of vilazodone rely upon a dual mechanism, acting as a SSRI in addition to its properties as a selective presynaptic 5-HT_{1A} receptor agonistic [12]. In 2002, a study reported AD-like effects of this compound on animals [13], and a first randomized, double-blind, placebo-controlled trial was published in 2009 [14], indicating that the treatment induced relief after 1 week of treatment. This drug was approved by the FDA in 2011. Finally, the AD effects of agomelatine [15] relate to the synergy between its action as an agonist of the melatonergic MT1 and MT2 receptors and its antagonistic action on the 5-HT_{2C} receptors [16]. The compound was approved for the treatment of depression in Europe in 2009.

As explained above, all the marketed ADs ultimately increase monoamines such as serotonin and norepinephrine, even though in some cases additional mechanisms may contribute to their action (e.g. melatonin). Furthermore, this involvement seems causal as serotonin depletion using *para*-chlorophenylalanine completely blocks the effects of SSRIs [17,18]; moreover, mice with a genetic deletion of the 5-HT_{1A} receptor become insensitive to the effects of fluoxetine, while they still respond to imipramine [19,20]. Similarly, Cryan et al. [20] demonstrated that mice unable to synthesize norepinephrine and adrenaline due to a targeted disruption of the dopamine β-hydroxylase gene (Dbh−/−) did not respond to the NRIs desipramine and reboxetine; the MAOI pargyline; or several SSRIs including fluoxetine, sertraline, or paroxetine, although the effects of citalopram, another SSRI, were present.

Paradoxically, however, the effects of ADs on monoaminergic neurotransmission is detected immediately after drug administration, while the therapeutic effects of the molecules appear at a later onset, usually following several weeks of chronic treatment [21]. This suggests that downstream mechanisms may account for the AD's ability to achieve remission. A number of biology-based theories have been proposed to explain this finding, which include progressive down-regulation of post-synaptic serotoninergic and noradrenergic receptors, enduring desensitization of the auto-receptors located on monoaminergic cell bodies and enhanced synaptic plasticity in some crucial brain areas. Neuropsychology-based theories have also been proposed. Of particular interest is the proposal that ADs may have some very rapid effects, such as remediating the negative affective bias present in depressed patients, which in turn could improve positive emotional processing and social relations, subsequently several weeks later leading to improved mood [22]. For example, in healthy volunteers, acute SSRI and NRI treatments improved positive emotional bias and processing of social cues [23–25], whereas in depressed patients, a single dose of reboxetine counteracted the negative biases seen in facial expression recognition and emotional categorization, an