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Review article

The role of serotonergic, adrenergic and dopaminergic receptors in antidepressant-like effect

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ABSTRACT

Depression is a serious global illness, becoming more and more common in developed countries. Because of specific symptoms it is considered as a leading cause of disability all over the world with a high death factor due to suicides. There are many antidepressants used in the therapy, but still more than 30% of patients do not respond to the treatment. The heterogeneous nature of the illness and its complex, unclear aetiology may be responsible for these difficulties. Next to the main monoaminergic hypothesis of depression there are also many other approaches connected with the pathophysiology of the disease, including hypothalamic–pituitary–adrenal axis dysregulation, dopaminergic, cholinergic, glutamatergic or GABA-ergic neurotransmission. Nevertheless, it can be unambiguously stated that serotonergic, noradrenergic and dopaminergic systems are precisely connected with pathogenesis of depression, and should be therefore considered as valuable targets in patients' treatment. Bearing that in mind, this review presents the role of serotonergic, adrenergic and dopaminergic receptors in antidepressant-like effect.

Contents

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Introduction

Major depressive disorder (MDD) is common and serious problem in modern society, and is responsible for disability worldwide. Sadness, lost of interest or pleasure, disturbed sleep and appetite, feelings of tiredness, low self-esteem or poor concentration are one of the main depressive symptoms, which strongly impair the individual's ability to function or cope with daily life, and sometimes can even lead to suicide. Currently one in four people in the world is affected by depression [1]. It is assumed that until 2020 it will be the second most commonly diagnosed disease in the world, just after ischaemic heart disease [1]. Despite the fact that there are many available antidepressants and possible therapies, there is still a problem with the efficacy of the treatment. It is very likely that this problem is associated with the complexity, and still not fully understood pathomechanism of the disease.

Since 1965 the monoaminergic theory of depression was considered as the main and only cause of the illness. This hypothesis assumed that MDD is connected with serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine; NA) deficits in different parts of the brain, and therefore the enhancement of serotonergic and noradrenergic neurotransmission, will result in the improvement of the common symptoms of the disease [2]. Over the years this theory has evolved, and many new approaches appeared. Scientists noticed the strong relationship between depressive state and changes in various systems not only serotonergic and noradrenergic but also dopaminergic, cholinergic, glutamatergic, GABA-ergic or hypothalamic–pituitary–adrenal (HPA) axis dysregulation. This review will discuss the role and involvement of serotonergic, adrenergic and dopaminergic receptors in antidepressant-like (AD-like) effect.

Animal tests and models of depression

First and foremost, it should be clarified that there is a difference between a test and a model of depression. A model includes both an independent variable (induced manipulation), and a dependent variable (behavioural/neurochemical readout), while a test simply comprises the latter variable [3,4].

There are two commonly used tests to assess AD-like activity – forced swim test (FST) and tail suspension test (TST). Both are based on the observation that when rodents are subjected to an inescapable situation, after the initial attempts to escape, the animals quickly adopt immobile posture [5,6]. It is believed that this change of behaviour (*i.e.* immobility) is reflecting behavioural despair. It has been shown that clinically effective antidepressants significantly decrease the immobility time in the FST and TST in rodents [7–11]. The FST, which was introduced by Porsolt et al., is a useful method for behavioural studies of rodents (mice [12] and rats [13]); reduced immobility score suggests the efficacy of the treatment. Since there were many reports on the lack of AD-like effect of SSRIs in the rat FST [14] (*e.g.* citalopram [15], fluoxetine [16], fluvoxamine [15] or paroxetine [17]), a modified version of the test was introduced [18]. In the modified version of the rat FST, three parameters are measured – immobility (analogously as in the original version of the test), swimming and climbing behaviours [18]. It has been demonstrated that compounds acting *via* serotonergic system increase swimming, whereas noradrenergic agents increase climbing behaviours [18]. The second very commonly used test – the TST, was designed as simpler and faster way to examine behavioural response to antidepressants [19]. The TST has many advantages over the FST, such as the lack of hypothermic effects of cold water, the ability to test animals with motor deficits, and increased sensitivity to a wider range of antidepressant compounds [20]. The main difference between these tests is that TST is not sensitive for the $GABA_B$ receptor antagonists and knockout (KO) mice [21].

Several models of MDD have been developed so far [3]. Since the aetiology of MDD is still poorly understood, it is not possible to base models solely on the aetiology. Therefore, three general strategies are considered: genetic manipulation, selective breeding for behavioural extremes, and environmental, physical, or pharmacological manipulations or a combination of the above [3].

Olfactory bulbectomy (OB) is a lesion model of depression. After surgical removal of the olfactory bulbs, both endocrinal and behavioural alterations, resembling MDD symptoms, can be noticed [22]. OB rats exhibit hyperactivity in the open field test and passive avoidance learning deficit; antidepressants reduce those behavioural changes to the normal level.

In the learned helplessness (LH) model, rodents are exhibited to unpredictable stressors (*e.g.* electrocution) [22]. As a result, animal's ability to avoid aversive stimuli is impaired in comparison with the behaviour under controllable stressors. This paradigm seems to be parallel to the symptoms of depression [22].

It is thought that chronic mild stress (CMS) model is probably the most veracious model of the MDD [22,23]. In brief, exposure of rats and mice to the uncontrollable, mild stressors induce endocrinal changes that produce behavioural effects *e.g.* anhedonia (a measurable parameter: decrease in the sucrose solution intake) [22,24].

Flinders sensitive line (FSL) rat is the model based on selective breeding. Studies revealed that FSL rats exhibit certain behavioural (reduced appetite and psychomotor function, normal hedonic responses and cognitive function, an altered circadian rhythm), neurochemical (changes in serotonergic, cholinergic, dopaminergic systems and neuropeptide Y, but normal HPA axis and GABA-ergic regulation), and pharmacological features that have been reported in depressed individuals [25,26].

Wistar-Kyoto (WKY) rat strain is another example of the animal model based on selective breeding. WKY rats exhibit several hormonal (dysregulation of the HPA axis), behavioural (hyperreactivity to stress), and physiological abnormalities, which are similar to those found in depressed individuals [27]. Moreover, WKY rats exhibit a depressive-like behaviour in a wide range of behavioural tests [27].

Furthermore, there are also genetically engineered mice, which enable the investigation of the functional consequences of silencing or overexpressing candidate genes that are thought to contribute to the pathophysiology of the disease.

It is noteworthy that some new optogenetic models of MDD have been introduced recently [25]. Using optogenic techniques various behaviours can be successfully manipulated *i.e.* hedonic and anhedonic-like behaviours [28], reward-seeking behaviours