Pharmacological Reports 69 (2017) 546–554

Contents lists available at ScienceDirect

Pharmacological Reports

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

Review article

The role of melatonin, neurokinin, neurotrophic tyrosine kinase and glucocorticoid receptors in antidepressant-like effect

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ARTICLE INFO

Article history:
Received 9 November 2016
Accepted 24 January 2017
Available online 29 January 2017

Keywords:
Melatonin receptors
Neurokinin receptors
Tropomyosin receptor kinase B
Glucocorticoid receptors
Antidepressant-like effect

ABSTRACT

Over the last few decades, depression has become one of the major public health problems in our society. This problem is connected not only with morbidity, but also with treatment, specifically with the effectiveness of the therapy as well as the concomitant side effects of available antidepressants. Major depressive disorder is a complex clinical entity, including different molecular mechanisms and neurological processes. This complexity is a challenge for scientists seeking to discover an innovatory antidepressant drug with multiple and complementary mechanisms of action. In this review, we discuss the role of melatonin, neurokinin, neurotrophic tyrosine kinase and glucocorticoid receptors in depression and antidepressant-like effects.

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Introduction

Major depressive disorder is a debilitating disorder, the etiology of which remains unknown, thereby it is difficult for clinicians to treat it properly and effectively. Previous papers discussed the involvement of many different mechanisms in the pathophysiology of this disease, including serotonergic, adrenergic, dopaminergic, glutamatergic, GABA-ergic and cholinergic receptors [1,2]. Each of these receptors may contribute to the development of depression as well as mediating antidepressant-like effects. Researchers are striving to acquire pertinent data to explain the complicated neuropsychological changes in major depressive

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http://dx.doi.org/10.1016/j.pharep.2017.01.026
1734-1140/

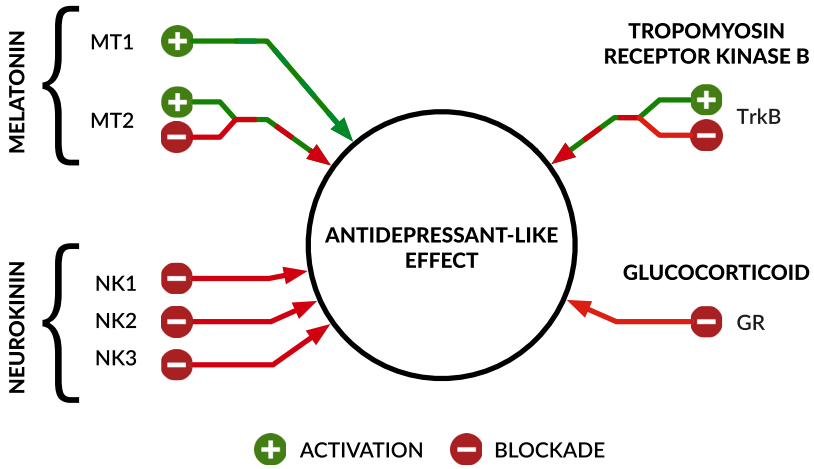

Fig. 1. The involvement of melatonin, neurokinin, neurotrophic tyrosine kinase and glucocorticoid receptors in antidepressant-like effect observed in animals.

disorder. Every new target provides an opportunity to discover an alternative treatment for the current problems with pharmacotherapy. This review presents the role of melatonin and neurokinin receptors and the hypothalamic-pituitary-adrenal (HPA) axis in depression and antidepressant-like effect, as well as the neurotrophic theory of depression (Fig. 1).

Melatonin and melatonin receptors

Melatonin, a tryptophan derivative, is a neurohormone synthesized in the pineal gland of vertebrates. Its main physiological action includes an impact on circadian rhythms. Melatonin is primarily secreted at night; hence, it is referred to as "the signal of darkness" [3]. The main regulator of melatonin secretion is the suprachiasmatic nucleus located in the hypothalamus [4]. We differentiate two types of receptors activated by melatonin: MT1 and MT2 [5]. Both of these are G-protein-coupled. Activation of melatonin receptors is commonly linked with many functions, not only connected with the light-dark cycle, but also immune response, vasodilatation or vasoconstriction as well as cell proliferation [6]. Agonism toward melatonin receptors may also result in antidepressant activity [7]. Several pharmacological agents (agomelatine, ramelteon and tasimelteon) that act via melatonin receptors and exert different activities are available on the market [7–9].

For the present study, agomelatin represents the most interesting activity as it works as an antidepressant agent [7]. This compound activates both types of melatonin receptors; additionally, it is an antagonist of 5-HT_{2C} serotonin receptors. It is one of the novel antidepressants approved for the treatment of major depression in adult patients by the European Medicines Agency in 2009 [7]. The introduction of agomelatin opened a new pathway in the treatment of depression – the impact on melatonin receptors. Here, we present a review of the role of MT1 and MT2 receptors in depression and in its treatment.

The activation of melatonin receptors is connected with several signal transduction pathways, often depending on the type of cells [3]. A decrease in the level of cyclic adenosine monophosphate (cAMP) may occur as an effect of inhibition of adenylyl cyclase by agonists of both melatonin receptors. Also, the stimulation of MT2 receptors leads to an increase in the activity of protein kinase C and an elevation in the level of cyclic guanosine monophosphate (cGMP) (a result of stimulation of guanylyl cyclase) [3,10].

Studies have proved that circadian rhythms may be involved in evoking disorders connected with mood, including depression [11]. *Post-mortem* studies conducted by Wu et al. [11] found specific up-regulation of MT1 receptors, but not MT2, in suprachiasmatic nucleus occurs in patients suffering from depression as a result of reduced melatonin levels. Hence, the authors suggested that potential antidepressant drugs acting on the melatonergic system should be focused primarily on MT1 receptors (as their agonists). On the other hand, contrasting reports also suggest the involvement of MT2 receptors in the pathogenesis of depression and several other disorders, including sleep disturbances and anxiety [12,13]. Hirsch-Rodriguez et al. [14] introduced an interesting assumption that the pattern of both melatonin receptor expression and their dimerization (MT1/MT2) might exert an effect on antidepressant treatment with the use of clomipramine, desipramine and fluoxetine. Also, endogenous melatonin has been proposed as improving the antidepressant action evoked by those medications in their extended application.

In animal studies, an important role of MT1 receptors has been reported. Adamah-Biassi et al. [15] investigated the effects of genetic deletion of MT1 in C57BL/6 mice and found a significant increase in the immobility time parameter for MT1-knockout animals in the forced swim test (both males and females). Additionally, those mice presented anxiolytic-like behaviors, which were assessed in the marble-burying test. Weil et al. [16] achieved similar results in the forced swim test: MT1-knockout mice spent significantly more time floating (i.e. being "immobile") than their wild-type counterparts. Also, in an assay investigating anxiolytic-like activity, the open field test, wild-type mice achieved "better" results than MT1-knockout ones, spending significantly more time in the central part of the arena. Noseda et al. [17] investigated the role of the modulation of MT2 receptors in antidepressant-like effect in the rat model of Parkinson's disease (evoked by the intranigral administration of rotenone). Using both a selective agonist and antagonist of MT2 receptors in the striatum, the authors assessed antidepressant-like activity in the forced swim test: the MT2 antagonist (4-P-PDOT) significantly reduced immobility and increased swimming time parameter and this effect was potentiated by rapid eye movement sleep deprivation [17].

There are few data concerning novel melatonin receptor ligands with antidepressant-like activity. In the study performed by Sumaya et al. [18], luzindole, an MT1 and MT2 antagonist, evoked antidepressant-like action in the forced swim test on C3H/HeN mice. Furthermore, this effect was mediated by blocking MT2 rather than MT1 receptors. A synthetic melatonergic compound, piromelatine, which is currently being tested for use in insomnia, was endowed with antidepressant potential in the rat model chronic mild stress [19].