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Review article

Serotonin transporter and receptor ligands with antidepressant activity as neuroprotective and proapoptotic agents

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ABSTRACT

Serotonin exhibits multiple non-neural functions involved in essential hypertension, early embryogenesis, follicle maturation and behaviour. The growth stimulatory effects of the neurotransmitter have been described for a variety of cell types. 5-HT was found to induce migration of the human prostate cancer cell lines – PC-3 and Du145 – and several 5-HT_{1A} antagonists and serotonin reuptake inhibitors were reported to inhibit the growth of different tumour cell lines *in vitro*. Recent studies suggest that neurogenesis is involved in the action of antidepressants and an involvement of antidepressants in adult hippocampal neurogenesis has been demonstrated. Antidepressants also exhibit neuroprotective activity, which could be connected to their antidepressant activity. However, it has been reported that certain antidepressants may induce apoptosis in some cancer cell lines. In the present paper the neuroprotective and proapoptotic activities of serotonergic antidepressants (SSRIs and TCAs), as well as 5-HT_{1A} receptor ligands are summarized and discussed based on biochemical transduction pathways associated with these activities.

Contents

Abbreviations: AC, adenylate cyclase; ADP, adenosine diphosphate; BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CHO, Chinese hamster ovary; CNS, central nervous system; CREB, cAMP response element binding; DAG, diacyloglicerol; ERK, extracellular signal-regulated kinase; FoxO, forkhead box O transcription factor; GABA, γ-amino butyric acid; GDNF, glial-derived nerve factor; GIRK, inwardly-rectifying potassium channel; GPCR, G protein coupled receptor; GTP, guanosine triphosphate; HEK, human embryonic kidney; 5-HT, 5-hydroxytryptamine; IFN-γ, interferone-γ; IκB, inhibitory protein of nuclear transcription factor κB; IL, interleukine; JNKc, Jun N-terminal kinase; KO, knockout; LPS, lipopolisaccharide; MAO, monoaminooxidase; MAPK, mitogen activated protein kinase; MDD, major depressive disorder; MDMA, 3,4-methylenedioxymethamphetamine; MDR, multidrug resistance/resistant; mGluR, metabotropic glutamatergic receptor; NF-κB, nuclear transcription factor κB; NK, neurokinine; Nrf2, NF-E2-related factor-2; NSC, neural stem cells; 8-OH-DPAT, 8-hydroxy-(2-*di*-*n*-propyloamino)tetralin; PC, prostate cancer; PI3K, phosphatidylinositol-3-kinase; PLC, phospholipase C; RNA, ribonucleic acid; ROS, reactive organic species; RSK, ribosomal S6 kinase; SARI, serotonin receptor antagonists and reuptake inhibitors; SERT, serotonin transporter; siRNA, small interference RNA; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TDZ, trazodone; TNFα, tumour necrosis factor α; TRK, tyrosine kinase receptor.

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Introduction

One of the main goals of medicinal chemistry is to design a reliable model of a molecular target involved in pathological changes and to identify potential ligands that are able to modify the pharmacological activity of an organism in a desired direction. However, as we have started to learn, addressing only one molecular target is often not sufficient for reversing the biochemical pathways responsible for pathological changes. For example, schizophrenia drugs that are designed as non-selective for selected molecular targets (referred as 'magic shotguns', 'multifunctional drugs' or 'intramolecular polypharmacy') are supposed to lead to new and more effective pharmacological treatments (for a review see [1]). A very complicated view also appears for the pharmacotherapy of depression, in which several molecular targets such as serotonin, dopamine, noradrenaline, $GABA_B$, mGlu, NK, nicotinic (and several others) receptors are postulated [2]. Thus, a challenge for medicinal chemistry is to identify potential molecular targets, and to propose multifunctional ligands for the identified molecular targets, or selective ligands for the different targets. It should be noted, that the complete mechanisms of action of known antidepressants have not been elucidated in detail. Antidepressant drugs have been shown to exhibit neuroprotective activity, which could be related to their antidepressant activity [3]. However, some antidepressant drugs may induce apoptosis in some cancer cell lines. In the present paper we discuss the neuroprotective and proapoptotic activity of the serotonergic antidepressants.

Serotonergic biochemical pathways involved in neuroprotection and apoptosis

5-HT as a prosurvival agent

In the mammalian central nervous system (CNS) serotonin elicits diverse physiological responses as a neurotransmitter or neuromodulator by interacting with various receptor subtypes [4]. Serotonin exhibits multiple non-neural functions that are involved in essential hypertension, early embryogenesis, follicle maturation and behaviour [5]. Ligands for the serotonergic system have been found to be involved in the regulation of different CNS diseases, including depression. The growth stimulatory effects of 5-HT have been described for a variety of cell types including vascular smooth muscle cells, lung fibroblasts, renal mesangial cells, normal as well as transformed intestinal epithelial cells, pancreatic carcinoid cells and small cell lung carcinoma [6] (and references therein), [7]. 5-HT is also a marker of neuroendocrine differentiation in prostatic carcinoma [6,8] and has been suggested to participate in the autocrine loops of growth factors that contribute to the proliferation of different cancer types and may thus be considered as an autocrine factor [9]. It was also found to behave as a growth factor in some nontumoural cells and recently found to be related to oncogenes [5].

The growth-stimulating and behavioural 5-HT activity was found to be connected to biochemical pathways such as MAPK, (MEK)/ERK, Akt and NF-κB. MEK inhibitors produce a number of changes in animal behaviour such as anxiolytic/anxiogenic effects, hyperactivity or depressive-like actions, as well as blocking the behavioural action of antidepressants [10–14]. Blockade of MAPK signalling also inhibits the behavioural effects of antidepressant drugs and induces a pro-depressive phenotype. The (MEK)/ERK pathways are involved in transcriptional/translational activation in neuronal survival and neuroplasticity in depression. ERK also activates the transcription factor CREB which plays a role in stress, anxiety, and depression [14]. After activation of the MAPK/ERK pathway apoptosis can be inhibited by phosphorylation of the proapoptotic protein Bad and by increased expression of the antiapoptotic Bcl-2. Hence the MAPK/ERK pathway may be involved both in the etiopatogenesis of depression and antidepressant drug efficacy.

5-HT was found to dose-dependently induce proliferation as well as ERK1/2 and Akt activation in PC-3 and Du145 cells. The MAPK inhibitor U0126 and the PI3K inhibitor LY294002 as well as the $5\text{-}HT_{1A}$ receptor antagonist NAN-190 were found to reverse these changes to different degrees [15]. 5-HT also induced migration of PC-3 and Du145 cells, which was inhibited by UO126 and LY294002. 5-HT can induce activation of two interrelated biochemical pathways MAPK/ERK and PI3K/Akt, and thus promote proliferation, differentiation and migration. It should also be noted that MAPKs may participate in growth and survival and therefore be important for the regulation of plasticity and the development of the CNS (for a review see [16]).

Dual role of NF-κB

NF-κB, which may play an important role in the regulation of serotonergic mechanisms, can be activated by different stress conditions (such as neurotoxins or oxidative stress) [17–22], and thus upregulate the expression of pro-apoptotic genes [23]. NF-κB activation may contribute to excitotoxin- and dopamine-induced apoptosis in neural cells [24,25] and the suppression of NF-κB activity may be neuroprotective [26–29]. NF-κB has been shown to help mouse hippocampal HT22 cells to resist oxidative stress [18] and to activate neuroprotective genes [30]. PI3K/Akt and ERK signalling may exhibit differential effects on NF-κB activation. In a CHO cell line stably expressing the human $5\text{-}HT_{1A}$ receptor the PI3K/Akt pathway was found to lead to downstream activation of NF-κB (by inhibiting IκBα subunit), followed by NF-κB nuclear translocation and inhibition of caspase-3 activity. In contrast, PI3K/Akt activation and NF-κB transcriptional activity was inhibited by agonist-dependent activation of ERK signalling [31]. In studies of cell survival, platelet-derived growth factor receptor-stimulated NF-κB was found to exhibit both antiapoptotic and proapoptotic activity: apoptosis was activated by the Raf/MAPK pathway while antiapoptosis was activated by the PI3K/Akt pathway [32,33]. As stated in two recent reviews [34,35], the diverse functions of NF-κB depend on the subunits of the formed NF-κB dimer. Thus, by coordinating the subunit constitution in the formation of a dimer, NF-κB can regulate transcription of different genes (including genes related to antiapoptotic, apoptotic, and inflammatory processes) and the effects of NF-κB on neuron survival or death depend on the activation of distinct NF-κB factors [34].