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Abstract

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New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates--Nrf2 activators and GSK-3 inhibitors.

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Abstract

This paper reviews new drug targets in the treatment of depression and new drug candidates to treat depression. Depression is characterized by aberrations in six intertwined pathways: (1) inflammatory pathways as indicated by increased levels of proinflammatory cytokines, e.g. interleukin-1 (IL-1), IL-6, and tumour necrosis factor α. (2) Activation of cell-mediated immune pathways as indicated by an increased production of interferon γ and neopterin. (3) Increased reactive oxygen and nitrogen species and damage by oxidative and nitrosative stress (O&NS), including lipid peroxidation, damage to DNA, proteins and mitochondria. (4) Lowered levels of key antioxidants, such as coenzyme Q10, zinc, vitamin E, glutathione, and glutathione peroxidase. (5) Damage to mitochondria and mitochondrial DNA and reduced activity of respiratory chain enzymes and adenosine triphosphate production. (6) Neuroprogression, which is the progressive process of neurodegeneration, apoptosis, and reduced neurogenesis and neuronal plasticity, phenomena that are probably caused by inflammation and O&NS. Antidepressants tend to normalize the above six pathways. Targeting these pathways has the potential to yield antidepressant effects, e.g. using cytokine antagonists, minocycline, Cox-2 inhibitors, statins, acetylsalicylic acid, ketamine, ω3 poly-unsaturated fatty acids, antioxidants, and neurotrophic factors. These six pathways offer new, pathophysiologically guided drug targets suggesting that novel therapies could be developed that target these six pathways simultaneously. Both nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activators and glycogen synthase kinase-3 (GSK-3) inhibitors target the six above-mentioned pathways. GSK-3 inhibitors have antidepressant effects in animal models of depression. Nrf2 activators and GSK-3 inhibitors have the potential to be advanced to phase-2 clinical trials to examine whether they augment the efficacy of antidepressants or are useful as monotherapy.

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