



Future Directions in the Biomedical Treatment of Depression

Glen Baker

Neurochemical Research Unit, Department of
Psychiatry, University of Alberta, Edmonton

- Most currently available prescription antidepressant drugs affect reuptake, metabolism and/or receptor activity of the biogenic amine neurotransmitters 5-hydroxytryptamine (5-HT, serotonin) and/or noradrenaline (NA).
- These drugs are associated with response and remission rates lower than desired, excessive adverse effects and prolonged periods before clinical improvement occurs.



- Results using elegant neuroimaging, molecular biological, neurochemical and pharmacological techniques have identified several exciting new possible targets for the development of future novel antidepressants.



Other possible antidepressant targets

- Dopamine (DA) (drugs that affect 5-HT, NA and DA simultaneously are also under investigation)
- GABA and glutamate: although rapid clinical antidepressant response still remains elusive, recent studies with the NMDA glutamate receptor antagonist ketamine are promising (although ketamine has adverse effects).



Other possible antidepressant targets (cont'd)

- neuroactive steroids (rapid acting steroids that act as allosteric modulators at GABA and/or glutamate receptors). For example, allopregnanolone has anxiolytic and antidepressant properties, and its brain levels have been reported to be increased by antidepressants.



Other possible antidepressant targets (cont'd)

- Components of the hypothalamic-pituitary-adrenal (HPA) axis with a focus on corticotrophin releasing factor (CRF). Antagonists of CRF receptors are being investigated as antidepressants.
- Substance P – neurokinin 1 receptor antagonists may have antidepressant properties.



Other possible antidepressant targets (cont'd)

- Cytokines and the immune system – Depression may be related to excessive amounts of proinflammatory cytokines. Studies in this area may clarify the role of glial cells in depression.
- Melatonin – agomelatine, an agonist of MT₁ and MT₂ receptors and an antagonist of serotonin 5-HT_{2c} receptors, has antidepressant properties.



Other possible antidepressant targets (cont'd)

- Signaling cascades, neurotrophic factors, neurogenesis: cyclic AMP-response element binding protein (CREB), brain-derived neurotrophic factor (BDNF).



- The systems mentioned above do not operate in isolation, and there is a need for funding groups with multidisciplinary expertise to conduct comprehensive studies on the interactions among these systems in depression and when screening potential new antidepressants.



- Neuroimaging studies (MRI, MRS, fMRI) have provided useful tools for understanding structural and functional changes in brain areas, and, when combined with studies on some of the systems mentioned above, should lead to more effective diagnosis and tracking of improvement in depression.



Important factors to consider in future biomedical studies in depression:

- comorbidity
- gender studies in depression
- deep brain stimulation
- epigenetic regulation (regulation of gene activity without altering the DNA code) in depression



Important factors to consider in future biomedical studies in depression (cont'd.):

- pharmacogenetics (the science dedicated to the identification of genes influencing response to pharmacotherapy) and personalized antidepressant treatment – e.g. genes related to receptors for and metabolism of biogenic amines; cytochrome P450 (CYP) enzymes involved in drug metabolism



Important factors to consider in future biomedical studies in depression (cont'd.):

- metabolomic approaches to define biomarkers
- herbal products and nutraceuticals
- the need for better animal models
- the neuroprotective properties of some antidepressants
- team approaches



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