Neurochemical Trends in Antidepressant Research: Moving Past the Monoamine Hypothesis

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Introduction. For over six decades, the monoamine hypothesis has shaped antidepressant pharmacotherapy, yet growing evidence challenges its comprehensiveness. This review seeks to evaluate the most recent scientific research and find emerging theoretical and practical neurochemical trends for treating depression.

Methods. A systematic search on PubMed found 22 reviews (published in the last 5 years) analyzing neurochemical mechanisms and treatments for depression. The articles, including systematic reviews and meta-analyses, were summarized and analyzed regarding their conclusions and recommendations on neurochemical depression treatments.

Results. Ten studies argue that serotonin's role in depression lacks consistent empirical support, with one claiming that classical SSRIs decrease serotonin levels. Alternative pathways are increasingly explored, with nine studies highlighting the significance of glutamate modulation through (S)-ketamine, NMDA antagonists, and dextromethorphan/buproprion (DXM/BUP) as rapid-onset antidepressants. Five studies underscore the role of GABAergic modulation and neurosteroids, particularly brexanolone, in mood regulation. Additionally, four studies identify inflammation and oxidative stress as potential targets, suggesting the therapeutic value of antioxidants and anti-inflammatory treatments (including a novel suggestion – stingless bee honey, SBH). Other emerging areas include brain-derived neurotrophic factor (BDNF) driven synaptic plasticity, mitochondrial function, mesenchymal stem cells, psychedelics and neuromodulation.

Conclusion. These findings emphasize the trend beyond a monoamine-centric perspective toward a multi-system approach in antidepressant development and prescription. Notably, several emerging treatments, such as ketamine and DXM/BUP, have already been approved for clinical use in the U.S., underscoring the growing shift toward exploring alternative neurochemical pathways.