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Imaging of serotonin synthesis and brain serotonergic receptors and their relation to affective disorders**Mirko Diksic**

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The study of regional serotonin synthesis in humans by imaging could enable researchers to obtain a better understanding of affective disorders and to develop better therapies.

Objective: To perform imaging of regional brain serotonin (5-HT) synthesis with labelled α -methyl-L-tryptophan [α -MTrp] in the normal and affected brain, as well as in the animal models of depression.

Methods: Studies were performed on laboratory animals using two different rat models of depression, where the synthesis was measured by autoradiography, and a ¹⁴C and ³H-labelled tracer. Positron emission tomography (PET) with a ¹¹C-labelled tracer was used in the human studies, on both normal subjects and on patients with various brain disorders (e.g., epilepsy, depression, obsessive compulsive disorder, borderline personality disorder, and those suffering from migraines). The patients met the DSM-IV criteria for depression or bipolar disorder (BPD), a disorder characterized by affective lability and impulsive aggressive behavior.

Results: The experiments in rats have shown that 5-HT synthesis is elevated in bulbectomized rats (using a model of agitated depression) and reduced in the Flinders Sensitive Line rats (using a model of retarded depression), and that antidepressants (e.g., citalopram, bupropion) have the effect of returning the synthesis to the level of the control rats without having a significant effect on plasma Trp concentration. The drugs have different effects following chronic and acute administration. The data suggest that 5-HT synthesis is differently controlled in the terminal areas than in the cell bodies. The results indicate that in healthy women, when compared to healthy men, serotonin synthesis is significantly lower in the right parietal lobe, bilateral middle frontal gyri, and bilateral parieto-occipital lobe. When comparing synthesis in the male BPD subjects to the male controls, we found a lower synthesis level in the anterior cingulate and left temporal lobe of the male BPD subjects, while the synthesis in the BPD subjects was higher in the posterior cingulate.

Conclusion: In depressed patients, we found a significant bilateral decrease in the anterior cingulate (ACC) (females), in the left ACC (males), and in the left mesial cortex (both gender). In addition, we have shown that antidepressants have region specific influence on 5-HT synthesis. In rat models of depression was shown that antidepressant produces changes in 5-HT synthesis and some 5-HT receptor sites. Some of these correlate with behavioural changes. The evaluation and imaging of regional synthesis, using α -MTrp as a tracer, is an excellent methodology for studying changes in brain 5-HT synthesis and the regional effects of drugs, in normal patients and in those with affective disorders which can help in discovery of new drugs and new treatment modalities.

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