Fenfluramine Stimulation of Serum Cortisol in Patients with Major Affective Disorders and Healthy Controls: Further Evidence for a Central Serotonergic Action of Lithium in Man*

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With 1 Figure

Received April 9, 1984; revised August 30, 1984

Summary

In order to investigate the influence of lithium long-term medication on serotonergic neurotransmission, fenfluramine stimulation (FFS) was used for the assessment of hormonal effects under serotonergic control. The cortisol plasma concentration following FFS was examined between 8 a.m. and 1 p.m. in 11 manic-depressive subjects under lithium prophylaxis and in 8 untreated euthymic patients. In addition, 11 healthy subjects with FFS, and 12 other subjects without FFS were investigated. The basal cortisol concentrations show considerable variation. Those of the lithium patients were in general found lower than those of the control groups. In both, the controls and the manic-depressive patients without lithium medication, no gross deviation from the expected physiological decline of morning cortisol values was found. A subtle effect of FFS in healthy subjects could be observed. In the lithium patients, however, a significant inversion of the cortisol secretion pattern with a steep increase between 10 and 12 a.m. could be demonstrated. It is concluded that FFS and lithium long-term medication exert an agonistic influence onto central serotonergic neurotransmission. Pharmacological challenge with fenfluramine may prove to be a useful tool for the investigation of serotonergic mechanisms in biological psychiatry.

* Partial results of this study were presented at the 3rd World Congress of Biological Psychiatry, Stockholm 1981.
Introduction

The mode of action of lithium prophylaxis in patients with manic-depressive disease is still unknown. Nevertheless, a vast body of experimental evidence has accumulated during the last decades giving rise to the assumption that the prophylactic effect of lithium may be partly related to its effect on central serotonergic neurons (for review ref. Müller-Oerlinghausen, in press). Yuwiler et al. (1979) described an elevated tryptophan-concentration in the brain after lithium treatment; moreover, Mandell and Knapp (1976) demonstrated that lithium differentially stimulates the central 5-HT metabolism and equilibrates the bilateral asymmetry in mesostriatal serotonin metabolites (Mandell and Knapp, 1979). Lithium has also been reported to increase the 5-HT syndrome in rats pretreated with tricyclic antidepressants (De Montigny et al., 1981; quoted from Bunney and Garland, 1983).

Chronic application of lithium decreases serotonin receptor binding sites in the hippocampus indicating an enhancement of serotonergic activity, which is followed by receptor subsensitivity in this area (Maggi and Euna, 1980; Treiser and Kellar, 1980).

Murphy et al. (1969) and Born et al. (1980) showed that chronic lithium treatment up to three months increased the serotonin uptake in blood platelets of manic-depressive patients. Coppen et al. (1980) reported an increased uptake of platelets 5-HT after lithium treatment of six weeks, one year, and after lithium prophylaxis of 4.3 years on average. This was confirmed by Meltzer et al. (1983), who reported a significant increase of 5-HT uptake after lithium treatment of at least one year duration.

Eroglu and Atamer-Simsek (1980) demonstrated a lithium-induced increase of cerebral serotonin in stress-exposed rats. Broderick and Lynch (1982) showed a significant reduction of muricidal behaviour in killer-rats. These findings may be related to the modulatory effect of lithium and 5-HT on aggressiveness in humans and animals (Brown et al., 1979; Brown et al., 1982; Mühlbauer, in press).

At present, published experimental and clinical results are difficult to compare as they were obtained by either acute or long-term treatment, in human or animal experiments, and either regional or total cerebral amount of serotonin was considered.

Invasive methods of investigation on central serotonin metabolism, e.g. the determination of 5-HIAA in cerebro-spinal fluid are rather unsuitable for repeated clinical investigations in patients. Therefore, we looked for an indicator system possibly reflecting central-nervous serotonergic activity, based on reliable laboratory