J. Neural Transmission 61, 81–94 (1985)

Journal of
Neural Transmission

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*

H. D. Mühlbauer and B. Müller-Oerlinghausen

Department of Psychiatry, Laboratory of Clinical Psychopharmacology, Free University of Berlin

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 decennies 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 *Enna,* 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

methods and convenient for investigations in an out-patient population.

We hypothesized that changes of a hormonal system under serotonergic control which are induced by a central serotonin agonist should be a possible approach. The circadian cortisol-secretion pattern which is regulated, at least partly, by serotonergic mechanisms (*Müller et al.*, 1977), was, therefore, investigated under the experimental condition of fenfluramine stimulation (FFS). This drug, fluormethylamphetamine, represents an anorectic agent highly selectively affecting well-known serotonergic pathways ascending from brainstem neurons to the forebrain (*Garattini et al.*, 1975; *Sotelo* and *Zamora*, 1978; *Duhault et al.*, 1975, 1979).

Methods

Characteristics of Patients and Controls

The following groups of subject were examined under fasting conditions:

Group 1:

12 healthy subjects (6 females, 6 males; mean age [m ± S.D.] 30.5 ± 4.5 years) *without* fenfluramine stimulation.

Group 2:

11 healthy subjects (7 females, 4 males; mean age m = 44.1 ± 12.7 years) *with* fenfluramine stimulation.

Group 3 and 4:

Group 3:

11 manic-depressive patients in the symptom-free interval under lithium prophylaxis *without* fenfluramine stimulation (7 females, 4 males; unipolar 4, bipolar 7; mean age 45 ± 14.5 years; duration of lithium treatment 6.3 ± 4.4 years; lithium serum concentration 0.66 ± 0.15 mmol/l; 2 patients received 150 μg per day, and 75 μg per day l-thyroxine, respectively).

Group 4:

The above mentioned 11 manic-depressive patients in the symptom-free interval under lithium prophylaxis investigated *with* fenfluramine stimulation three months later.

Group 5:

8 manic-depressive patients without any acute psychiatric symptomatology, psychotropic medication, or previous lithium medication *with* fenfluramine stimulation (6 females, 2 males; unipolar 4, bipolar 4; mean age 44.3 ± 13.5 years).

After the initial blood sampling at 8 a.m., the experimental groups received 60 mg fenfluramine-HCl orally. Blood samples were taken by an indwelling intravenous catheter (butterfly system) at 9, 10, 11, 12 a.m., 1 p.m., and at 8 a.m. next day. Due to a technical fault four blood samples at 1 p.m. could not be assessed in group 5. (Therefore, these values are not shown in Fig. 1.) The controls without fenfluramine stimulation consisted of healthy subjects, in whom blood was collected at 8, 10, and 12 a.m., and at 8 a.m. the next day.

Informed consent was obtained from all subjects.

Biochemical Assay

The blood was centrifuged, and the serum deep-frozen. The cortisol concentration was determined by radio-immuno-assay (double antibody method). The inter-assay variance is 13 %, the intra-assay variance 6 %. Cross-reactions for corticosterone are 1.5 % and for cortisone 1 %, respectively. All the other physiologically existing steroid hormones show a cross-reactivity of less than 0.1 %.

Blood glucose assessments were performed by the glucose oxidase methode (Beckman glucose analyzer II).

Data Analysis

An analysis of variance for repeated measurements (ANOVA) was used to evaluate temporal effects (decline of cortisol concentrations) in different groups (1, 2, 3, 5) and interactions between treatments groups and temporal effects. To compare different groups at specific periods, non-parametric tests for paired (*Wilcoxon*-test) and non-paired samples (*Mann-Whitney*-test) were used. A two-tailed level of significance was used. All values are expressed as mean ± S.E.M.

Results

1. Basal Cortisol Concentrations at 8 a.m.

The group means of the 8 a.m. fasting cortisol concentrations before administration of fenfluramine differed considerably, and

Table 1. *Analysis of variance for repeated measurements of morning cortisol concentrations in treatment groups 1, 2, 3, 5*

	F	df	p
Groups	16.47	2	< 0.001
Course of morning cortisol	4.01	6	< 0.001
Groups × course	1.22	12	$= 0.278$

showed a large inter-individual variance. Comparing all five groups with each other, a statistically significant difference is found between group 3 and group 1 ($p < 0.05$) as well as between group 3 and 2 ($p < 0.01$). Group 4 differs from group 2 significantly ($p < 0.01$). The difference between group 3 and 4, *i.e.* identical patients investigated at different times, does not reach statistical significance. The difference between the two independent control groups, however, is statistically significant (group 1 versus group 2; $p < 0.05$).

2. Course of Morning Cortisol Concentrations

The course of the morning cortisol concentrations in group 1, 2, 3, and 5 shows the physiological decline of this hormone. The results of ANOVA for repeated measurements (Table 1) show a significant difference of all groups ($p < 0.001$), possibly due to the differing initial cortisol concentrations, and a significant change of cortisol concentrations during the observed period ($p < 0.001$). There is no interaction of groups and course ($p = 0.278$), which implies a similar temporal pattern in all groups. The difference between 8 a.m. cortisol concentrations of group 1 ($p < 0.001$), 2, 3, 5 ($p < 0.01$), and those at 12 a.m. is statistically significant. Furthermore, the decline between 10 a.m. and 12 a.m. in group 1 is significant ($p < 0.05$).

At variance with the groups mentioned above, a different pattern of morning cortisol is observed under FFS in lithium patients. After an initial fall of cortisol concentrations, a sharp rise of cortisol occurs at 10 a.m., not corresponding to the physiological decline of this hormone ($p = 0.002$; Fig. 1). Table 2 shows the significant differences of morning cortisol between patient groups with and without FFS at 11 a.m. and 12 a.m. Furthermore, there is a significant ($p = 0.0013$) difference between group 1 and 4. Table 3 summarizes the findings in all groups.

3. Blood Glucose Concentration

As fenfluramine is known to produce hypoglycemia, which again is a common cause for a rise in cortisol concentration, the

Table 2. *Significant differences of morning cortisol (p refers to 11 a.m.; 12 a.m.) between group 3, 4, 5 (patients with and without FFS (*Mann-Whitney-*test)*

Group	3	4
4	$p < 0.01$; 0.01	–
5	$p < 0.05$; 0.16	$p < 0.05$; 0.01

Table 3. *Basal -cortisol and secretion pattern in lithium long-term patients, manic-depressive patients and controls with and without fenfluramine (60 mg orally) (nmol/l h-cortisol; $\bar{x} \pm S_{\bar{x}}$)*

Time (a.m.)	8.00	9.00	10.00	11.00	12.00	13.00	8.00
Group 1 (Controls without fenfluramine)	589.0 ±91.1		411.0 ±47.0		310.7 ±42.2		613.3 ±69.0
Group 2 (Controls with fenfluramine)	689.7 ±46.9	611.5 ±47.4	655.5 ±40.9	548.5 47.2	500.2 ±32.0	448.3 ±35.5	698.0 ±54.2
Group 3 (Lithium patients without fenfluramine)	386.6 ±49.9	388.9 ±13.7	326.0 ±24.0	295.9 ±35.6	295.2 ±31.6	303.5 ±30.4	414.1 ±57.6
Group 4 (Lithium patients with fenfluramine)	496.3 ±48.0	387.7 ±29.3	363.9 ±25.6	466.4 ±57.3	478.7 ±32.2	424.0 ±32.7	533.5 ±37.5
Group 5 (manic-depressives with fenfluramine)	585.8 ±86.4	466.6 ±71.1	366.9 ±37.0	334.1 ±20.8	360.8 ±50.4	444.6 ±79.7	539.1 ±43.2

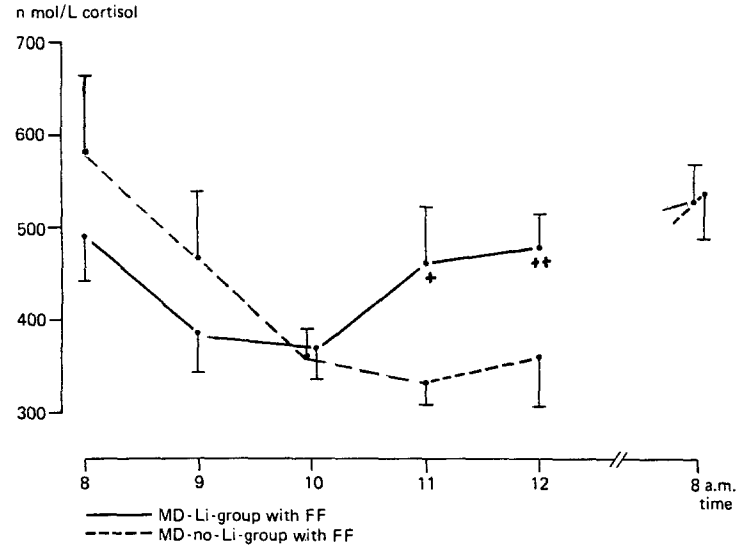

Fig. 1. Basal h-cortisol and morning excretion pattern. Lithium treated (MD-Li-Group; Group 4) *vs.* untreated manic-depressives (MD-no-Li-Group; Group 5) with fenfluramine stimulation (FFS) ($\bar{x} \pm S_{\bar{x}}$); * $p < 0.05$, ** $p < 0.01$

morning pattern of blood glucose was determined. The average decline of 9 % did not reach statistical significance. It seems very unlikely that these changes in blood glucose could cause the change of the cortisol secretion in the different groups between 8 a.m. and 1 p.m.

Discussion

Fasting Cortisol Concentrations at 8 a.m.

Platman and *Fieve* (1968), *Platman et al.* (1971), *Berens* and *Wolff* (1975), *Müller-Oerlinghausen et al.* (1977), *Halmi et al.* (1978), *Czernik* and *Kleesiek* (1979) did not observe any significant differences of basal cortisol plasma concentrations in lithium treated manic-depressive patients, although an initial, but transient rise after acute oral administration was evidenced.

We found a significantly lower basal cortisol concentration in the lithium treated patients (group 3) compared with both control groups. Nevertheless, there is a considerable inter- and also intra-individual variation of cortisol levels; *e.g.* the lithium patients re-

examined three months later (group 4) exhibited this lowered basal concentration only when compared with control group 2 reflecting the significant difference of basal cortisol in the control groups themselves.

The reason for these differences is not clear. However, according to clinical observations during the FFS it is unlikely that the experimental stress, anticipation of the drug etc. could be responsible for the hormonal variability.

This variation may cast some doubt on cross-sectional evaluations of basal cortisol concentrations. Differential effects after specific endocrine stimulation have, therefore, gained considerable interest at present. Dexamethason-suppression, hypoglycemia, IV L-tryptophan infusion (*Charney et al.*, 1982, 1984; *Heninger et al.*, 1983), 5-hydroxytryptophan orally (*Meltzer et al.*, 1982; *Meltzer et al.*, 1984) etc. were chosen for the assessment of serotonergic function in man.

In our ongoing studies on the serotonergic effects of lithium prophylaxis (*Mühlbauer* and *Hardt*, 1980; *Mühlbauer et al.*, 1981; *Mühlbauer* and *Müller-Oerlinghausen*, 1982, 1984) we used fenfluramine as a central 5-HT challenge (*Garattini* and *Samanin*, 1976; *Duhault et al.*, 1975, 1979; *Clineschmidt et al.*, 1978; *Steranka* and *Sanders-Bush*, 1979; *Orosco et al.*, 1984). Furthermore, in contrast to other authors (*Meltzer et al.*, 1983, 1984) we took circadian changes of cortisol into account.

Some effects of fenfluramine on the central nervous system consist in anorectic activity (*Garattini* and *Samanin*, 1976), mild sedation (*Fink et al.*, 1971), and controversial influence on mania and depression (*Pearce*, 1973; *Cockson* and *Silverstone*, 1976; *Murphy et al.*, 1978).

There is conclusive evidence that fenfluramine acts on the serotonergic cell-bodies of the area B 9 of the lateral raphe system (*Blundell* and *Lesheim*, 1974; *Knapp* and *Mandell*, 1976; *Sotelo* and *Zamora*, 1978) with its ascending pathways to the basal ganglia, hypothalamus, and limbic system (*Rommelspacher* and *Strauss*, 1980). Although the role of the serotonergic system is far from being elucidated, there is converging evidence that it has homeostatic and pace maker functions (*Aghajanian* and *Wang*, 1978) as well as an important role in the circadian periodicity of ACTH and cortisol regulation (*Müller et al.*, 1977).

The Course of Morning Cortisol Concentrations

After the administration of fenfluramine, no alteration of the physiological decline of plasma cortisol over the whole period from 8 a.m. to 12 a.m. occurs in both, the healthy controls and the manic-

depressives without lithium prophylaxis. A significant decrease, however, between 10 and 12 a.m. can be observed only in the unstimulated controls. The fact that this is not observed in the stimulated controls is due to three subjects signaling a susceptibility to this kind of serotonergic challenge in some of the healthy subjects.

In contrast to this attenuation of the steepness of the hormonal decline in group 2, a significant inversion of the course of cortisol concentration starting at 10 a.m. is found in the lithium patients. Such effects are not observed neither without stimulation (group 3) nor in manic-depressives devoid of lithium treatment, but with FFS (Fig. 1).

Since the prophylaxis and not the underlying illness is the distinguishing feature, the increased susceptibility to FFS in lithium patients seems to be due to the lithium treatment. As cortisol release is regulated not only by serotonergic, but also adrenergic and possibly cholinergic influences it should be emphasized that fenfluramine does neither possess a marked adrenergic nor a cholinergic effect (*Garattini et al.*, 1975). Because of the questionable importance of dopamine onto cortisol secretion, its weak dopaminergic effect can be neglected.

Our findings are in line with the already existing evidence for serotonergic effects of lithium obtained in animal experiments (*Ahluwalia* and *Singhal*, 1981; *Broderick* and *Lynch*, 1982; *De Montigny et al.*, 1981; *Eroglu* and *Atamer-Simsek*, 1980; *Friedman et al.*, 1979; *Harrison-Read*, 1979; *Knapp* and *Mandell*, 1979; *Lerer et al.*, 1980; *Maggi* and *Enna*, 1980; *Mandell* and *Knapp*, 1976; *Poitou et al.*, 1974; *Sangdee* and *Franz*, 1980; *Swann et al.*, 1981; *Schubert*, 1973; *Treiser* and *Kellar*, 1980; *Yuwiler et al.*, 1979). Effects of lithium on 5-HT uptake in platelets were demonstrated also in man (*Murphy et al.*, 1969; *Born et al.*, 1980; *Coppen et al.*, 1980; *Corona et al.*, 1982).

The present study, however, provides strong evidence for central serotonergic effects of lithium in symptom-free manic-depressive patients. Our data are in accordance with *Meltzer et al.* (1983, 1984) reporting that in acutely ill manic and depressive patients lithium augmented the cortisol response to 5-hydroxytryptophan. *De Montigny et al.* (1983) and *Heninger et al.* (1983) demonstrated an increased antidepressant effect when lithium was added to tricyclic antidepressant treatment. They also discuss a serotonergic mode of action of lithium.

Conclusions

Since fenfluramine rather selectively stimulates cells of the raphe system, and lithium seems to potentiate the very subtle effect of FFS

observed in healthy subjects, it can be speculated that lithium also acts on serotonergic midbrain systems. Due to the auto-regulatory mechanisms of these 5-HT raphe cells any change of the firing rate increases or decreases collateral inhibition (*Aghajanian* and *Wang*, 1978). Thus, the band-width of this phylogenetically old system is extremely well-buffered. This may be the reason why unidirectional effects of lithium on central serotonergic mechanisms, *i.e.* tryptophan metabolism (*Knapp* and *Mandell*, 1979; *Mandell* and *Knapp*, 1976, 1979), changes of receptor sensitivity or density (*Bunney* and *Garland*, 1983) etc. can be observed in long-term treated patients only by special provocation methods.

Though experimental evidence suggests that lithium affects simultaneously various specific brain regions and receptor systems, the putative mechanism of fenfluramine stimulation on one hand, and the normalizing effect of lithium treatment on elation and depression on the other hand give rise to the assumption that this simple alkali-ion also controls the bandwidth of serotonergic midbrain systems possibly related to manic-depressive illness. Finally, our preliminary results suggest that FFS warrants further investigation and may prove to be a useful tool for the investigation of serotonergic function in biological psychiatry.

Acknowledgement

Our thanks are due to the staff of ward 20 and 21 of the Neukölln-Hospital (Berlin). Ilse Becker, research nurse of our lithium clinic took care of the patients and was of immense help in performing this study. Gudrun Simons, Dipl.-Psych., provided statistical assistance.

References

Ahluwalia, P., Singhal, R. L.: Monoamine up-take into synaptosomes from various regions of rat brain following lithium administration and withdrawl. Neuropharmacol. *20*, 483–487 (1981).

Aghajanian, G. K., Wang, R. Y.: Physiology and pharmacology of central serotonergic neurons. In: Psychopharmacology: A Generation in Progress (*Lipton, A., Di Mascio, A., Killam, K. F.*, eds.), pp. 171–183. New York: Raven Press. 1978.

Berens, S. C., Wolff, J.: Lithium Research and Therapy, pp. 443–445. London-New York-San Francisco. 1975.

Blundell, J. E., Leshem, M.: Central action of anorexic agents: Effects of amphetamine and fenfluramine in rats with lateral hypothalamic lesions. European J. Pharmacol. *28,* 81–83 (1974).

Born, G. V. R., Grignani, G., Martin, K.: Long-term effect of lithium on the up-take of 5-hydroxytryptamine by human platlets. Br. J. Pharmacol. *9,* 321–325 (1980).

Broderick, P., Lynch, V.: Behavioral and biochemical changes induced by lithium and L-tryptophan in muricidal rats. Neuropsychopharmacol. *21,* 671–679 (1982).

Brown, G. L., Goodwin, F. K., Ballenger, J. C., Goyer, P. F., Major, L. F.: Aggression in human correlates with cerebrospinal fluidamine metabolites. Psychiat. Res. *1,* 131–139 (1979).

Brown, G. L., Ebert, M. H., Goyer, P. F., Jimerson, D. C., Klein, W. J., Bunney, W. E., Goodwin, F. K.: Aggression, suicide, and serotonin: Relationships in CSF amine metabolites. Am. J. Psychiat. *139,* 741–746 (1982).

Bunney, W. E., Garland, B. L.: Possible receptor effects of chronic lithium administration. Neuropharmacol. *22,* 367–372 (1983).

Charney, D. S., Heninger, G. R., Reinhard, J. F., Sternberg, D. E., Hafstead, K. M.: The effect of IV L-tryptophan on prolactin, growth hormone, and mood in healthy subjects. Psychopharmacol. *78,* 38–43 (1982).

Charney, D. S., Heninger, G. R., Sternberg, D. E.: Serotonin function and mechanism of action of antidepressant treatment. Arch. Gen. Psychiatr. *41,* 359–365 (1984).

Clineschmidt, B. V., Zacchei, A. G., Totaro, J. A., Pflueger, A. B., Mc Guffin, J. C., Wishousky, Th. I.: Fenfluramine and brain serotonin. Ann. N.Y. Acad. Sci. *305,* 222–241 (1978).

Cockson, J., Silverstone, T.: 5-hydroxytryptamine and dopamine pathways in mania. A pilot study of fenfluramine and pimozide. Br. J. Pharmacol. *3,* 942–947 (1976).

Coppen, A., Swade, C., Wood, K.: Lithium restores abnormal platlet 5-HT-transport in patients with affective disorders. Br. J. Psychiat. *136,* 235–238 (1980).

Corona, G. L., Cucchi, M. L., Santagostino, G., Frattini, P., Zerbi, F., Fenoglio, L., Savoldi, F.: Blood noradrenaline and 5-HT levels in depressed women during amitriptyline and lithium treatment. Psychopharmacol. *77,* 236–241 (1982).

Czernik, A., Kleesiek, K.: Neuroendokrinologische Veränderungen unter Langzeitbehandlung mit Lithiumsalzen. Pharmacopsychiat. *12,* 305–312 (1979).

De Montigny, C., Tan, A. T., Caille, G.: Short-term lithium enhances 5-HT neurotransmission in rat administered chronic antidepressant treatments. Presented at Society for Neuroscience, 11th Annual Meeting, Los Angeles, p. 646 (1981).

De Montigny, C., Cournoyer, G., Morisette, R., Langlois, R.: Lithium carbonate addition ot tricyclic antidepressant-resistant unipolar depression. Arch. Gen. Psychiat. *40,* 1327–1334 (1983).

Duhault, J., Beregi, L., Du Boistesselin, R.: General and comparative pharmacology of fenfluramine. Curr. Med. Res. Opin. *6,* 3–14 (1979).

Duhault, J., Malen, Ch., Boulanger, M., Voisin, C., Beregi, L., Schmitt, H.: Fenfluramine and 5-hydroxytryptamine. Arzneim.-Forsch./Drug Res. *25,* 1755–1762 (1975).

Eroglu, L., Atamer-Simsek, S.: Effect of lithium on stress-induced changes in brain levels of monoamines in rats. Arzneim.-Forsch./Drug Res. *30,* 2115–2117 (1980).

Fink, M., Shapiro, D. M., Itil, T. M.: EEG-profiles of fenfluramine, amobarbital, and dextroamphetamine in normal volunteers. Psychopharmacol. *22,* 369–383 (1971).

Friedman, E., Dallob, A., Gershon, L.: The effect of lithium long-term treatment on reserpine-induced supersensitivity in dopaminergic and serotonergic transmission. Life Sci. *25,* 1263–1266 (1979).

Garattini, S., Jori, A., Buczko, W., Samanin, R.: The mechanism of action of fenfluramine. Postgrad. Med. J. *51,* 27–35 (1975).

Garattini, S., Samanin, R.: Anorectic drugs and brain neurotransmitter. In: Appetite and food intake (*Silverstone, T.,* ed.), pp. 83–108. (Dahlem Workshop on Appetite and Food-intake.) Berlin: Abakon Verlagsgesellschaft. 1976.

Halmi, K. A., Noyes, R., Millard, S. A.: Effect of lithium on plasma cortisol and adrenal response to adrenocorticotropin in man. Clin. Pharmacol. Ther. *13,* 699–703 (1978).

Harrison-Read, P. E.: Evidence from behavioural reactions to fenfluramine, 5-hydrox-tryptophan, and 5-methoxy-N, N-dimethyltryptamine for differentia effects of short-term and long-term lithium on indoleaminergic mechanisms in rats. Br. J. Pharmacol. *66,* 144–145 (1979).

Heninger, G. R., Charney, D. S., Sternberg, D. E.: Lithium carbonate augmentation of antidepressant treatment. Arch. Gen. Psychiat. *40,* 1335–1342 (1983).

Heninger, G. R., Charney, D. S., Sternberg, D. E.: Serotonergic function in depression. Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. Arch. Gen. Psychiat. *41,* 398–402 (1984).

Knapp, S., Mandell, A. J.: Coincidence of blockade of synaptosomal 5-hydroxytryptamine uptake and decrease in tryptophan hydroxylase activity: Effects of fenfluramine. J. Pharmacol. Exp. Ther. *198,* 123–132 (1976).

Knapp, S., Mandell, A. J.: Lithium and chlorimipramine differentially alter bilateral asymmetry in mesocortical serotonin metabolites and kinetic conformation of midbrain tryptophan hydroxylase with respect to tetrahydrobiopterin cofactor. Neuropharmacol. *19,* 1–7 (1979).

Lerer, B., Ebstein, R. B., Felix, A., Belmaker, R. H.: Lithium amelioration of reserpine-induced hypoactivity in rats. Int. Pharmacopsychiat. *15,* 338–343 (1980).

Mandell, A. J., Knapp, S.: A neurobiological model for the symmetrical prophylactic action of lithium in bipolar affective disorder. Pharmacopsychiat. *9,* 116–126 (1976).

Mandell, A. J., Knapp, S.: Asymmetry and mood, emergent properties of serotonin regulation. Arch. Gen. Psychiat. *36,* 909–916 (1979).

Maggi, A., Enna, S.J.: Regional alteration in rat brain neurotransmitter systems following chronic lithium treatment. J. Neurochem. *34,* 888–892 (1980).

Meltzer, H. Y., Witta, B., Tricou, B.J., Simonovic, M., Fang, V., Manov, G.: Effects of serotonin precursors and serotonin agonists on plasma hormone levels. In: Serotonin in Biological Psychiatry (*Ho, B. T., Schoolar, J. C., Usdin, E.,* eds.), pp. 117–139. Raven Press. 1982.

Meltzer, H. Y., Arora, R. C., Baber, R., Tricou, B.J.: Serotonin uptake in blood platelets of psychiatric patients. Arch. Gen. Psychiat. *38,* 1322–1326 (1981).

Meltzer, H. Y., Arora, R. C., Goodnick, P.: Effect of lithium carbonate on serotonin uptake in blood platelets of patients with affective disorders. J. Affect. Disorders *5,* 215–221 (1983).

Meltzer, H. Y., Lowy, M., Robertson, A., Goodnick, P., Perline, R.: Effect of 5-hydroxytryptophan on serum cortisol levels in major affective disorders. Arch. Gen. Psychiat. *41,* 391–397 (1984).

Mühlbauer, H. D.: Human aggression and the role of central serotonin. Pharmacopsychiat. (in press).

Mühlbauer, H. D., Hardt, W.: The influence of lithium salts and antidepressive medication on the serum prolactin level. Pharmacopsychiat. *13,* 213–217 (1980).

Mühlbauer, H. D., Graef, K.J., Müller-Oerlinghausen, B.: Neuroendokrine Aspekte der Lithium-Prophylaxe. In: Biologische Psychiatrie (*Beckmann, H.,* ed.), p. 211–217. Stuttgart: G. Thieme. 1981.

Mühlbauer, H. D., Müller-Oerlinghausen, B.: The fenfluramine test: A simple tool for investigations on lithium-induced changes of serotonergic neurotransmission in manic-depressive patients. Arzneim.-Forsch./Drug Res. *32,* 897 (1982).

Mühlbauer, H. D., Müller-Oerlinghausen, B.: Veränderungen der serotonergen Neurotransmission bei manisch-depressiven Patienten unter Lithium-Prophylaxe. In: Forschungen zur Biologischen Psychiatrie (*Hopf, A., Beckmann, H.,* eds.), pp. 192–197. Berlin-Heidelberg-New York-Tokyo: Springer. 1984.

Müller, E. E., Nisticó, G., Scapagnini, U.: Neurotransmitters and Anterior Pituitary Function. New York-San Francisco-London: Academic Press. 1977.

Müller-Oerlinghausen, B.: Lithium long-term medication–does it act via serotonin? Pharmacopsychiat. (in press).

Müller-Oerlinghausen, B., Bauer, H., Girke, W., Kanowski, S., Goncalves, N.: Impairment of vigilance and performance under lithium treatment. Studies in patient and normal volunteers. Pharmakopsychiat. *10,* 67–78 (1977).

Murphy, D. L., Colburn, R. W., Davis, J. M., Bunney, W. E.: Stimulation by lithium of monoamine uptake in human platelets. Life Sci. *8,* 1187–1193 (1969).

Murphy, D. I., Slater, S., De la Vega, C. E., Lipper, S.: The serotonergic neurotransmitter system in the affective disorders–a preliminary evaluation

of the antidepressant and antimanic effects of fenfluramine. In: Neuropsychopharmacology (*Demker, P., Thomas-Radouko, C., Villeneuve, A.*, eds.), pp. 675–682. Oxford: Pergamon Press. 1978.

Orosco, M., Bremond, J., Jacquot, C., Cohen, Y.: Fenfluramine and brain transmitter in the obese zucker rat. Neuropharmacol. *23,* 183–188 (1984).

Pearce, J. B.: Fenfluramine in mania. Lancet *1, 800, 427* (1973).

Platman, St. R., Fieve, R. F.: Lithium carbonate and plasma cortisol response in the affective disorders. Arch. Gen. Psychiat. *18,* 591–594 (1968).

Platman, S. R., Hilton, J. G., Koss, M. C.: Production of cortisol in patients with manic-depressive psychosis treated with lithium carbonate. Dis. Nerv. Syst. *32,* 542–544 (1971).

Poitou, P., Guerinot, F., Bohoun, C.: Effect of lithium on central metabolism of 5-hydroxytryptamine. Psychopharmacol. *38,* 75 (1974).

Rommelspacher, H., Strauss, S.: Effect of lesions of raphe nuclei on the activity of catecholaminergic and serotonergic neurones in various brain regions of the rat *in vivo.* J. Neural Transm. *49,* 51–62 (1980).

Sangdee, C., Franz, D. N.: Lithium enhancement of central 5-HT transmission induced by 5-HT precursors. Biol. Psychiat. *15,* 59–75 (1980).

Schubert, J.: Effects of chronic lithium treatment on monoamine metabolism in rat brain. Psychopharmacol. *32,* 301–311 (1973).

Steranka, L. R., Sanders-Bush, E.: Species differences in the rate of disappearance of fenfluramine and its effects on brain serotonin neurons. Biochem. Pharmacol. *28,* 3103–3107 (1979).

Swann, A. C., Heninger, G. R., Roth, R. H., Maas, J. W.: Differential effects of short- and long-term lithium on tryptophan uptake and serotonergic function in cat brain. Life Sci. *28,* 347–354 (1981).

Sotelo, C., Zamora, A.: Lack of morphological changes in the neurons of the B 9 group in rats treated with fenfluramine. Curr. Med. Res. Opin. *6,* 55–62 (1978).

Treiser, S., Kellar, K. J.: Lithium: Effects on serotonin receptors in rat brain. Eur. J. Pharmacol. *64,* 183–185 (1980).

Yuwiler, A., Benett, B. L., Brammer, G. L., Geller, E.: Lithium treatment and tryptophan transport through the blood-brain barrier. Biochem. Pharmacol. *28,* 2709–2712 (1979).

Authors' address: Dr. *H. D. Mühlbauer,* Labor für Klinische Psychopharmakologie, Psychiatrische Klinik und Poliklinik der Freien Universität Berlin, Eschenallee 3, D-1000 Berlin 19.