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Review

Lithium and serotonin function: implications for the serotonin hypothesis of depression

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Abstract. Lithium enjoys wide clinical use in the treatment of affective disorders, but the mechanism of its action in these conditions is still controversial. Recent studies have shown that lithium can interact with other antidepressant drugs to enhance their efficacy, perhaps by specific effects on serotonin (5-HT) function. A large body of independent evidence suggests that 5-HT function is abnormal in depression. This review documents preclinical evidence of lithium's effects on 5-HT function at the levels of precursor uptake, synthesis, storage, catabolism, release, receptors, and receptor-effector interactions. The weight of this evidence suggests that lithium's primary actions on 5-HT may be presynaptic, with many secondary postsynaptic effects. Studies in humans, using very different methodological approaches, generally suggest that lithium has a net enhancing effect on 5-HT function. These actions of lithium may serve to correct as-yet unspecified abnormalities of 5-HT function involved in the pathogenesis of depression.

Key words: Lithium – Serotonin – Depression

Although lithium has figured prominently in the psychopharmacologic armamentarium for nearly 4 decades, its mechanism of action is still unknown. In part, this reflects the breadth of its clinical activity, with clear evidence of efficacy in the treatment of affective disorders, and suggested efficacy in schizophrenia, alcoholism, pathological aggression, migraine, granulocytopenia, thyrotoxicosis, and numerous other neuropsychiatric and medical conditions (Jefferson et al. 1987). Lithium has similarly wide-ranging effects on biological systems throughout the body, including the brain (Bunney and Garland-Bunney 1987; Wood and Goodwin 1987). Among the most extensively investigated of these central effects are those involving serotonin (5-HT) function, which are of special interest because of the putative role of 5-HT in the pathogenesis of affective disorders (Coppen 1967; Prange et al. 1974; Goodwin and Post 1983).

While lithium has long been known to have antidepressant effects, recent studies have shown that lithium can enhance the efficacy of primary antidepressants, with the suggestion that this enhancement may be mediated by 5-HT mechanisms (deMontigny et al. 1983; Heninger et al. 1983; Price 1989). In this paper, we will comprehensively review the preclinical and clinical research literatures on the effects of lithium on various aspects of central 5-HT function. We will additionally attempt to reconcile the disparate methodologies and findings reported in these literatures, with particular emphasis on the implications of available findings for understanding the interaction of lithium with 5-HT function in depression.

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Studies in animals

Precursor availability. The synthesis of 5-HT in the brain is dependent on the availability of its amino acid precursor, tryptophan. Many studies in laboratory animals show that tryptophan concentrations and/or uptake are increased in brain tissue or synaptosomes after both short-term (3–8 days) (Tagliamonte et al. 1971; Berggren 1987) and long-term (2–5 weeks) (Knapp and Mandell 1973; Swann et al. 1980, 1986) lithium treatment, whereas a single dose of lithium is without effect (Berggren 1985) (cf. Table 1). Failure to demonstrate increased brain tryptophan levels or uptake might be related to increased utilization (Poitou et al. 1974; Grahame-Smith and Green 1974) or regional variations (Ahluwalia and Singhal 1980; Yocca et al. 1983; Shukla 1985), and both of these factors may interact with duration of treatment (Swann et al. 1986). Lithium's effects on tryptophan uptake appear to be mediated by its ability to stimulate a high-affinity neuronal uptake system (Knapp and Mandell 1973; Herrero et al. 1983), since lithium does not affect the low-affinity neutral amino acid carrier of the blood-brain barrier (Yuwiler et al. 1979; Ehrlich et al. 1980). Induction of a more fluid state of the neuronal plasma membrane may be involved in this stimulatory process (Herrero et al. 1987). Evidence from rats suggests that long-term lithium may increase the responsiveness of tryptophan uptake to changes in 5-HT utilization (Swann et al. 1980); in cats, however, significant correlations between tryptophan uptake and 5-HT turnover are apparent only after short-term, but not long-term, lithium (Swann et al. 1986).

Brain 5-HT/5-HIAA concentration. Studies examining the effect of short-term (3–8 days) lithium treatment on brain or synaptosomal concentrations of 5-HT or its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have shown increases in one or both substances (Sheard and Aghajanian 1969; Perez-Cruet et al. 1971; Tagliamonte et al. 1971; Poitou et al. 1974; Minegishi et al. 1981; Berggren 1986) or no change (Schubert 1973; Collard and Roberts 1977; Minegishi et al. 1981; Atterwill and Tordoff 1982), with one

study reporting increases and decreases in different brain regions (Swann et al. 1986). Acute treatment (one or multiple doses within 28 h) with lithium has no effect on 5-HT concentrations (Corrodi et al. 1967; Furukawa et al. 1978; Vale and Ratcliffe 1987), but may increase 5-HIAA (Furukawa et al. 1978). Studies of long-term (3–6 weeks) lithium suggest that 5-HT and 5-HIAA concentrations decrease (Ho et al. 1970; Treiser et al. 1981; Karoum et al. 1986), although an increase in 5-HT has been reported (Cappeliez et al. 1982). Most contradictory are those studies examining the effects of intermediate-length (10–14 days) lithium: some have shown an increase in 5-HIAA, with levels of 5-HT either unchanged (Bliss and Ailion 1970; Collard and Roberts 1977; Collard 1978) or decreased (Shukla 1985), suggesting increased turnover of 5-HT. Other studies have reported decreased 5-HIAA (Swann et al. 1986), in one case with decreased 5-HT (Ahluwalia and Singhal 1980), in another with increased levels of 5-HT suggesting decreased 5-HT turnover (Reches et al. 1985).

Turnover. Some investigators have tried to clarify lithium's effects on brain 5-HT turnover and synthesis by experimentally altering normal metabolic processes. For example, some groups (Sheard and Aghajanian 1969; Hotta et al. 1986) have used probenecid, which blocks the exit of 5-HIAA from the brain, to show that the increase in 5-HIAA seen after short-term (4 days) lithium is caused by an increase in 5-HT synthesis and/or turnover, rather than by a decrease in outflow of 5-HIAA. An approach more frequently employed involves administration of a monamine oxidase (MAO) inhibitor to prevent the oxidative deamination of 5-HT to 5-HIAA, with measurement of the resulting increase in 5-HT or decrease in 5-HIAA used to calculate the rate of 5-HT turnover. Studies using this method have shown that short-term (3–5 days) lithium increases 5-HT turnover (Perez-Cruet et al. 1971; Grahame-Smith and Green 1974; Poitou et al. 1974; Minegishi et al. 1981; Atterwill and Tordoff 1982), while intermediate-length (14 days) (Bliss and Ailion 1970) and long-term (4 weeks) lithium have no significant effect on whole-brain turnover, despite significant regional changes [e.g., increases in cerebellum, decreases in hypothalamus (Ho et al. 1970)]. Unfortunately, this technique does not shed light on the reason for the increased turnover, for example, whether it derives from increased synthesis or from increased utilization of a particular catabolic pathway (viz., oxidative deamination).

Synthesis. Studies measuring the accumulation of 5-HTP after inhibition of aromatic amino acid decarboxylase suggest that 5-HT synthesis is decreased after a single dose of lithium (Berggren 1985), unchanged after 1–5 days of treatment (Berggren 1987), and increased after 8 days of treatment (Berggren 1986). Similarly, short-term (7 days) lithium enhanced the increase in labelled 5-HT and 5-HIAA after IV administration of ^{3}H-tryptophan (Schubert 1973), a finding replicated using unlabelled tryptophan loading in conjunction with MAO inhibition after 3 days of lithium (Minegishi et al. 1981). The activity of tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of 5-HT, appears to play a major regulatory role in this process. Since tryptophan hydroxylase is normally unsaturated, the availability of its substrate tryptophan may ultimately be the crucial factor in determining the rate of 5-HT synthesis.

Table 1. Effects of lithium treatment of differing duration on indices of 5-HT function in laboratory animals

5-HT functional index	Duration of lithium treatment									
	Acute (1 day)		Short-term (2–7 days)		Intermediate (8–14 days)		Long-term (≤ 21 days)			
	Increased	Unchanged	Decreased	Increased	Unchanged	Decreased	Increased	Unchanged	Decreased	Increased	Unchanged	Decreased
Precursor availability	–	1, 2	–	1, 3, 4, 5, 6[a]	6[a], 7, 8	6[a]	5, 6[a], 9	6[a], 10, 11	–	5, 12	13	–
Concentration:												
5-HT	–	14, 15, 16	–	3, 17, 18	4, 7, 19, 20, 21	–	9, 22[a]	10[a], 11[a], 19, 22[a], 23, 24	10[a], 11[a]	25	26[a], 27[a]	26[a], 27[a], 28
5-HIAA	–	16	–	3, 6[a], 7[a], 17, 18, 20	4, 6[a], 7[a], 19	6[a]	6[a], 9, 11[a], 19, 23, 24	6[a], 10[a], 11[a], 22[b]	10[a], 22[a]	–	28	–
Turnover	–	–	–	7[b], 8[b,c], 17[c], 18[b], 20[b], 21[b], 29[c]	–	–	–	23[b]	–	26[a,b]	26[a,b]	26[a,b]
Synthesis	–	–	2[d]	4[e], 5, 20[e]	1[d]	–	9[d]	5	–	–	5	–
Storage/release	–	30[f], 31	8, 32[f], 33[f]	34[a]	31, 34[a]	4, 19, 21	31	24	19	27[a], 31[a], 35	27[a]	31[a]
Uptake	–	–	–	–	–	–	–	–	36	–	27	–

Electrophysiology:												
Firing rate	–	37[f]	–	–	17, 38	–	–	–	–	–	–	–
Neurotransmission	39	–	–	38, 39, 40	–	–	–	–	–	–	–	–
Receptor binding:												
5-HT_1	–	41[a]	41[a]	–	29[a], 42	29[a], 43	–	29[a]	29[a]	–	27[a], 29[a], 41[a], 42[a]	27[a], 29[a], 41[a], 42[a], 43
5-HT_2	–	41	44[f]	–	–	29	–	45	29	–	27[a], 41	27[a], 29
Receptor-mediated responses:												
By receptor subtype:												
Nonspecific 5-HT	–	–	–	46, 47, 48, 49, 50	46, 47	8	–	–	–	46, 47	50, 51	–
5-HT_1	–	–	–	40[g], 48[g], 50[h]	40[g], 45[g h], 48[g h]	–	48[g]	45[h], 48[g h]	45[h]	–	–	50[h]
5-HT_2	–	89	–	–	–	45	–	–	29, 45	–	–	–
By receptor locus:												
Presynaptic	–	–	–	–	40, 45, 48	34	–	48	45	–	–	31, 35
Postsynaptic	–	–	–	40, 48, 50	38	–	48	–	–	–	–	50
Second-messenger effects												
cAMP	–	–	–	–	43	–	–	–	–	43	–	–
Inositol phosphates	–	–	52	–	53	–	–	–	52	–	–	–

[a] Effect varies by brain region
[b] Turnover assessed by increase in 5-HT or decrease in 5-HIAA after treatment with monoamine oxidase inhibitor
[c] Turnover assessed by increase in 5-HIAA after treatment with probenicid
[d] Synthesis assessed by increase in 5-HTP after inhibition of aromatic acid decarboxylase
[e] Synthesis assessed by increase in 5-HT and 5-HIAA after administration of tryptophan
[f] Lithium added in vitro
[g] 5-HT_{1a}-receptor-mediated response
[h] 5-HT_{1b}-receptor-mediated response

[1] Berggren (1987); [2] Berggren (1985); [3] Tagliamonte et al. (1971); [4] Schubert (1973); [5] Knapp and Mandell (1973); [6] Swann et al. (1986); [7] Poitou et al. (1974); [8] Grahame-Smith and Green (1974); [9] Berggren (1986); [10] Ahluwalia and Singhal (1980); [11] Shukla (1985); [12] Swann et al. (1980); [13] Yocca et al. (1983); [14] Corrodi et al. (1967); [15] Furukawa et al. (1978); [16] Vale and Ratcliffe (1987); [17] Sheard and Aghajanian (1969); [18] Perez-Cruet et al. (1971); [19] Collard and Roberts (1977); [20] Minegishi et al. (1981); [21] Atterwill and Tardoff (1982); [22] Reches et al. (1985); [23] Bliss and Ailion (1970); [24] Collard (1978); [25] Cappeliez et al. (1982); [26] Ho et al. (1970); [27] Treiser et al. (1981); [28] Karoum et al. (1986); [29] Hotta et al. (1986); [30] Saldate et al. (1975); [31] Friedman and Wang (1988); [32] Chase et al. (1969); [33] Katz and Kopin (1969); [34] Hotta and Yamawaki (1988); [35] Wang and Friedman (1988); [36] Ahluwalia and Singhal (1981); [37] Segal (1974); [38] Blier and deMontigny (1985); [39] Sangdee and Franz (1980); [40] Blier et al. (1987); [41] Tanimoto et al. (1983); [42] Maggi and Enna (1980); [43] Hotta and Yamawaki (1986); [44] Battaglia et al. (1983); [45] Goodwin et al. (1986a); [46] Harrison-Read (1979); [47] Harrison-Read (1981); [48] Goodwin et al. (1986b); [49] Meltzer et al. (1981); [50] Zohar et al. (1986); [51] Friedman et al. (1979); [52] Kendall and Nahorski (1987); [53] Butler and Barkai (1987)

As we have already seen, lithium treatment increases tryptophan uptake. Knapp and Mandell (1973) showed that lithium treatment for 3, 5, 10, and 21 days actually decreased rat midbrain tryptophan hydroxylase activity, but the simultaneous increase in tryptophan uptake resulted in enhanced conversion of tryptophan to 5-HT at 3 and 5 days, with return to baseline by 10 and 21 days. Nonsignificant decreases in rat midbrain tryptophan hydroxylase activity after 12 days of lithium have also been demonstrated by others (Ahluwalia and Singhal 1980). Knapp and Mandell (1973) initially hypothesized that the decrease in tryptophan hydroxylase activity was accomplished via nonspecific compensatory mechanisms. More recent evidence suggests that lithium may have complex direct effects on the enzyme's conformational and kinetic properties which permit higher levels of activity than would be expected in the face of other direct and indirect effects leading to increased negative feedback (Knapp and Mandell 1979, 1983). Inhibition of tryptophan hydroxylase by *p*-chlorophenylalanine abolishes the behavioral hyperactivity seen in lithium-treated rats after MAO inhibition, further suggesting an effect of lithium on 5-HT synthesis (Grahame-Smith and Green 1974).

Storage and release. Other evidence suggests that intraneuronal metabolism of 5-HT is enhanced by lithium. Collard and Roberts (1977) found that lithium treatment for 5 or 10 days inhibited the rise in 5-HT after intraperitoneal injection of tryptophan; the rise in 5-HIAA was unaffected after 5 days but enhanced after 10 days of lithium. These authors speculated that lithium might interfere with the vesicular storage of 5-HT, resulting in greater amounts of free cytoplasmic 5-HT available for breakdown by MAO to 5-HIAA. This hypothesis accounted for early observations that lithium added to rat brain slices in vitro seemed to diminish the electrically-induced release of 5-HT (Chase et al. 1969; Katz and Kopin 1969), as well for subsequent more technically refined work showing no effect of lithium (Saldate and Orrego 1975). In the first in vivo stimulation study, Collard (1978) also found that 10 days of lithium had no effect on the increased 5-HT and 5-HIAA concentrations produced by electrical stimulation of the midbrain raphe. However, failure of the 5-HT reuptake inhibitor clomipramine to abolish the increase in 5-HIAA concentration in lithium-treated animals led him to conclude that lithium might interfere with stimulus-release coupling so that 5-HT was released from storage vesicles into the cytoplasm rather than into the synaptic cleft. This formulation better accounts for evidence that short-term lithium can diminish release from storage sites (Schubert 1973), even though the increase in 5-HT after short-term lithium seems localized to cytoplasmic rather than vesicular synaptosomal fractions (Atterwill and Tordoff 1982). Treiser et al. (1981) found that long-term (4–6 weeks) lithium actually increased basal and KCl-stimulated 5-HT release in hippocampus, but not in cortex (Treiser et al. 1981). Friedman and Wang (1988) also reported that lithium increased KCl-stimulated 5-HT release in parietal cortex, hypothalamus, and hippocampus after 2 or 3 weeks of treatment, but not after a single injection or 1 week of treatment; basal 5-HT release was increased in hippocampus, decreased in hypothalamus, and unchanged in parietal cortex after 3 weeks, but unchanged throughout after short-term lithium. Hotta and Yamawaki (1988) found that short-term (3 days) lithium had no effect on basal 5-HT release in hippocampus or frontal cortex, whereas KCl-stimulated release was increased in hippocampus. Lithium's effects on intraneuronal storage and release of 5-HT do not appear to be mediated via the reserpine-sensitive 5-HT-binding vesicular protein (Reches et al. 1985).

Uptake. Lithium's effects on 5-HT uptake have not been reported extensively, but appear to be minimal compared to other antidepressant drugs. One study found evidence of diminished synaptosomal uptake after intermediate-length (12 days) lithium (Ahluwalia and Singhal 1981), whereas another reported no significant effect in hippocampus or cortex after long-term (4–6 weeks) lithium (Treiser et al. 1981).

Electrophysiology. Recent work indicates that, in some neural pathways, single-dose (Sangdee and Franz 1980) and short-term (2–3 days) (Sangdee and Franz 1980; Blier and deMontigny 1985; Blier et al. 1987) lithium can enhance 5-HT neurotransmission after electrical stimulation. However, the firing rate of 5-HT neurons is unaffected by short-term (2–4 days) lithium treatment (Sheard and Aghajanian 1969; Blier and deMontigny 1985), nor does iontophoretic application of lithium change the firing rate of postsynaptic hippocampal neurons (Segal 1974).

Receptor binding. Treiser et al. (1981) performed an integrative study, referred to above, showing that long-term (4–6 weeks) lithium decreased 5-HT_1 and putative 5-HT_2 receptor binding. Significant effects were observed only in hippocampus but not cortex (Harrison-Read 1979; Maggi and Enna 1980; Hotta et al. 1986), whereas 2 days of treatment has no effect (Maggi and Enna 1980). 5-HT_2 receptor binding has been reported to decrease in both cortex and hippocampus after as little as 7 and as much as 28 days of lithium (Hotta et al. 1986), although other evidence supports Treiser et al. (1981) in finding no effect of lithium on cortical 5-HT_2 density (Goodwin et al. 1986a). While none of these investigations observed changes in binding affinity, an in vitro study found that lithium decreased the affinity of 5-HT for 5-HT_2 receptors (Battaglia et al. 1983).

Receptor-mediated responses: by receptor subtype. The functional implications of these receptor changes are complex. Investigation of this issue has generally involved the measurement of putative 5-HT-receptor-mediated physiological or behavioral responses to 5-HT agonists. Thus, high doses of lithium given acutely, either as single or multiple hourly injections, induce a characteristic head-twitch response that is markedly affected by concomitant drugs which enhance or diminish 5-HT function (Wielosz and Kleinrok 1979; Yamada and Furukawa 1979), with blockade of the response by the 5-HT_2 antagonist ketanserin (Hotta et al. 1986). Short-term (3–5 days) lithium has been variously reported to increase, decrease, and leave unchanged the 5-HT_2-mediated hyperactivity response to 5-methoxy-N,N-dimethyltryptamine (Grahame-Smith and Green 1974; Harrison-Read 1979, 1981; Goodwin et al. 1986a, b), with similar disparity in results after longer-term (2–6 weeks) treatment (Friedman et al. 1979; Harrison-Read 1979, 1981; Goodwin et al. 1986a). An equally inconsistent pattern of results has been reported for the hyperactivity response to 5-HTP (Harrison-Read 1979, 1981; Goodwin

et al. 1986a, b; Hotta et al. 1986), but the PRL response to both 5-HT and N,N-dimethyltryptamine has been found to be increased after short-term (4 days) lithium (Meltzer et al. 1981).

Receptor-mediated responses: by receptor locus. The most recent studies have attempted to clarify the roles of pre- versus postsynaptic receptors in mediating the effects of lithium on 5-HT function. Goodwin et al. (1986a) reported that 14, but not 3 days of lithium attenuated the hypothermic response to the 5-HT_{1A} agonist 8-hydroxy-2(di-n-propylamino)tetralin (8-OH-DPAT) in mice, suggesting diminished presynaptic receptor function. In rats, however, the same authors found that 3–14 days of lithium enhanced the postsynaptic hyperactivity response to 8-OH-DPAT while leaving the presynaptic hypothermia response unchanged (Goodwin et al. 1986b). In both studies, motor responses to the putative 5-HT_{1B} agonist RU 24969 were unaffected. Zohar et al. (1986) reported that short-term (3–5 days) lithium enhanced the anorexia induced by fenfluramine and the putative 5-HT_{1B} agonist *m*-chlorophenylpiperazine (*m*-CPP), whereas long-term (21–23 days) lithium attenuated the effect of *m*-CPP but not fenfluramine, with no change in motor activity.

Using microiontophoretic and electrophysiological techniques, Blier and deMontigny (1985) found that 2 days of lithium did not alter the effects of 5-HT applied to rat hippocampal neurons, but increased the response of the same neurons to electrical stimulation of the ventromedial 5-HT pathway, suggesting a primary presynaptic mechanism for this effect. This group also found that 3 days of lithium in rats did not alter the responsiveness of presynaptic terminal autoreceptors, assessed with methiothepin, or somatodendritic autoreceptors, assessed with *d*-lysergic acid diethylamide (LSD) and 8-OH-DPAT, whereas a subset of postsynaptic 5-HT_{1A} receptors showed increased sensitivity (Blier et al. 1987). Blier et al. (1987) suggested that these postsynaptic receptors might control 5-HT neuronal firing via a feedback loop, since inhibitory presynaptic autoreceptors did not seem to be directly affected by lithium.

Hotta et al. (1986) observed that 3 or 7 days concurrent administration of lithium and the putative 5-HT autoreceptor antagonist methiothepin enhanced the lithium-induced diminution in hippocampal 5-HT_1 and cortical 5-HT_2 receptor binding, and augmented the increase in 5-HT turnover. These authors suggested that blockade of inhibitory presynaptic 5-HT autoreceptors resulted in enhanced accumulation of 5-HT in the synaptic cleft, with resulting down-regulation of postsynaptic receptors. Consistent with this, Hotta and Yamawaki (1988) showed that the inhibitory effect of 5-HT on the KCl- or electrically-evoked release of [^{3}H]5-HT, presumably mediated by presynaptic autoreceptors, was attenuated in hippocampus, but not frontal cortex, after 3 days of lithium treatment. These findings contradict those of Blier et al. (1987), but are consistent with Friedman and Wang (1988), who used methiothepin, LSD, and 5-methoxytryptamine to show desensitization of autoreceptor function after long-term (21 days) lithium.

Second-messenger effects. A burgeoning literature has begun to clarify the intracellular consequences of 5-HT receptor activation, with particular emphasis on the cyclic adenosine monophosphate (cAMP) and phosphoinositide (PI) systems as major effector mechanisms (Sanders-Bush and Conn 1987). While many studies have documented effects of lithium on these second-messenger systems (Bunney and Garland-Bunney 1987; Wood and Goodwin 1987), few have examined these effects with specific reference to 5-HT. Long-term (3 weeks), but not short-term (5 days), lithium increased 5-HT-stimulated cyclic adenosine monophosphate (cAMP) formation despite decreased 5-HT_1 receptor binding, an effect that did not appear to be mediated via changes in receptor-enzyme coupling (Hotta and Yamawaki 1986). Presumably reflecting 5-HT_2 receptor function, acute (one injection) and intermediate-length (2 weeks) lithium treatment decreased 5-HT-stimulated accumulation of [^{3}H]inositol phosphates in one study (Kendall and Nahorski 1987), but other investigators found no effect after one week of treatment (Butler and Barkai 1987).

Summary. Preclinical studies show that lithium's effects on 5-HT function occur at a variety of levels, including precursor uptake, synthesis, storage, catabolism, release, receptors, and receptor-effector interactions. Many effects are time dependent or region specific, and variations between species are observed. Some effects which appear to oppose each other probably reflect the operation of compensatory homeostatic mechanisms. Overall, these findings suggest that lithium's primary actions are on presynaptic function, with postsynaptic changes perhaps more secondary in nature. In laboratory animals, lithium's net effect seems to be an enhancement of 5-HT function.

Studies in humans

In comparison with the extensive animal literature, clinical studies of lithium's effects on 5-HT function are relatively limited in number and design. Three major paradigms have been utilized.

Cerebrospinal fluid (CSF) metabolite studies. Change in the level of lumbar CSF 5-HIAA before and after lithium treatment has been used as an index of change in central 5-HT turnover. Although these levels are determined by the interaction of several factors, including spinal cord 5-HT neuronal activity and removal of 5-HIAA and other acid metabolites from the CSF, evidence indicates that a significant fraction of lumbar CSF 5-HIAA is derived from central 5-HT processes (Banki and Molnar 1981). A number of studies have reported CSF 5-HIAA levels to be lower in depressed patients than in healthy controls, but some investigators have found no difference between groups, leading to the suggestion that low CSF 5-HIAA levels may be limited to a subgroup of depressed patients with a history of suicidal or other impulsive behavior (Goodwin and Post 1983; Meltzer and Lowy 1987).

Many early CSF studies are difficult to interpret because of limitations in experimental design and hypothesis formulation. For example, Sjostrom and Roos (1972) reported no effect of lithium on CSF 5-HIAA in manic patients, but they failed to utilize a within-subjects design and many of their patients received neuroleptics. Similarly, Mendels et al. (1972) examined changes in CSF monoamine metabolite levels from the perspective of clinical state rather than drug effects, so their observation of a marked lithium-induced increase in CSF 5-HIAA was limited to only one manic patient. However, other early reports involving very

small numbers of manic patients suggested that lithium increased CSF 5-HIAA (Mendels 1971; Wilk et al. 1972).

Larger studies have generally shown that lithium increases CSF 5-HIAA. Fyro et al. (1975) observed a significant increase compared with pretreatment levels after 12 days of lithium in 13 manic or hypomanic patients. Bowers and Heninger (1977) reported a similar effect after a mean 27 days of lithium in 23 mixed affective disorder patients. Berrettini et al. (1985) found that 12 euthymic bipolar patients had higher CSF 5-HIAA levels during maintenance lithium treatment than they did drug-free at least 2 weeks after lithium discontinuation. Swann et al. (1987) reported that ten manic patients had higher CSF 5-HIAA levels after 18 days of lithium than before treatment, but the difference was not statistically significant. Bowden et al. (1988) also found nonsignificantly higher CSF 5-HIAA levels in 15 manic patients after 4 weeks of lithium than before treatment, whereas levels in 13 unipolar depressed were unchanged.

Platelet 5-HT function studies. A large number of studies have examined 5-HT function in the blood platelet as a peripheral-tissue analogue of similar mechanisms in central neurons (Stahl 1977). The special relevance of this model for studying lithium's effects is enhanced by strong evidence that platelet 5-HT uptake, as reflected in the number of platelet 5-HT uptake sites (V_{max}), is decreased in affective disorder patients (Tuomisto and Tukiainen 1977; Scott et al. 1979; Born et al. 1980; Coppen et al. 1980; Meltzer et al. 1983; Stahl et al. 1983).

Lithium added to platelet-rich plasma in vitro does not affect (Born et al. 1980; Meltzer et al. 1983; Lingjaerde 1977) or decreases (Coppen et al. 1980) 5-HT uptake. In contrast, chronic lithium treatment of affective disorder patients has generally been shown to increase 5-HT uptake in platelets, with few consistent effects on the affinity for 5-HT (K_m) of the uptake sites. Born et al. (1980) found that uptake in ten bipolar patients maintained on lithium for at least 3 months was greater than uptake in eight mixed affective disorder patients not on lithium and equivalent to uptake in ten matched controls; however, both lithium-treated and -untreated patients were also receiving other antidepressant, anxiolytic, or neuroleptic drugs. Coppen et al. (1980) reported that uptake in 28 euthymic unipolar depressed and 7 euthymic bipolar patients receiving lithium for a mean 4.3 years was greater than uptake in 26 drug-free depressed and 25 drug-free remitted depressed patients. Separate analyses showed that groups of euthymic patients receiving lithium for 6 weeks or for 1 year both had greater uptake than remitted drug-free depressed patients. Murphy et al. (1969) found that uptake increased in nine mixed affective disorder patients after 1 week of lithium treatment. In contrast, Scott et al. (1979) observed no change in uptake after lithium treatment lasting 5 days or 3 weeks in seven healthy controls or lasting 5 days, 3 weeks, or 3 months in a "small group" of mixed affective disorder patients. Meltzer et al. (1983) reported that shorter-term lithium treatment (2–3 weeks) further decreased the already diminished baseline uptake in 14 bipolar manic and 7 bipolar depressed patients, whereas very long-term treatment (>1 year) produced the increase in uptake reported by other investigators. Consistent with this, Poirier et al. (1988) found that uptake was decreased in seven healthy controls after 10 and 20 days of lithium treatment.

Goodnick et al. (1984) reported that discontinuation of chronic (4.4 ± 2.2 years) lithium treatment in 11 euthymic bipolar patients produced a decrease in platelet 5-HT uptake compared with on-lithium baseline, but this effect required 3 weeks to become apparent. Poirier et al. (1988) found that lithium discontinuation in their healthy subjects resulted in an initial persistence of the lithium-induced decrease in uptake lasting 1 week, followed by a return to baseline by week 2, and a rebound increase above baseline in some subjects that began at week 5 and continued at least through week 10. The relatively gradual onset and offset of lithium's effects on the 5-HT uptake site suggested by these data are consistent with the hypothesis that such effects might be related to changes in 5-HT receptor sensitivity, which also occur gradually over time. Lithium-induced 5-HT_2 receptor supersensitivity has been inferred on the basis of an enhanced 5-HT-provoked aggregatory response in platelets from a mixed group of 24 affective disorder patients receiving lithium for a mean 5.5 years compared with 23 healthy controls and 22 drug-free depressed patients (Wood et al. 1985). However, Glue et al. (1986) observed that lithium treatment of eight healthy subjects for 4 and 20 days had no effect on platelet binding of iodinated LSD, another putative measure of 5-HT_2 receptors.

5-HT function in the platelet has also been assessed by measuring the high-affinity binding of [^{3}H]-imipramine (IMI) to a site which is believed to function as a modulator of 5-HT uptake. Many studies have found the number (B_{max}) of platelet [^{3}H]-IMI binding sites to be decreased in depressed patients compared to healthy subjects (Meltzer and Lowy 1987). The effects of lithium on [^{3}H]-IMI binding are still ambiguous. Although [^{3}H]-IMI binding in human platelet membranes was not affected by in vitro incubation with lithium (Poirier et al. 1988), 5 weeks of lithium treatment in rats caused a decrease in brain [^{3}H]-IMI binding (Plenge and Mellerup 1982). Baron et al. (1986) reported that platelet [^{3}H]-IMI binding was lower in 33 euthymic bipolar patients maintained on lithium for 3–15 years than in 58 healthy controls; these authors interpreted this as a trait marker for bipolar disease rather than an effect of chronic lithium. However, Goodnick et al. (1984) stated that platelet [^{3}H]-IMI binding in seven of their lithium-maintained euthymic bipolar patients was "within normal limits" and unaffected by lithium discontinuation, while Meltzer et al. (1984a) reported no effect of lithium in an unspecified number of newly hospitalized psychiatric patients. Similarly, Poirier et al. (1988) observed no change in platelet [^{3}H]-IMI binding after 20 days of lithium treatment or after lithium discontinuation in their seven healthy subjects.

Neuroendocrine challenge studies. The third major paradigm used in humans has involved examination of lithium's effects on neuroendocrine responses to in vivo pharmacologic challenges with agents believed to increase 5-HT function. Initial studies have found differences between affective disorder patients and normal controls in the neuroendocrine responses to the 5-HT releaser fenfluramine (Siever et al. 1984), the 5-HT precursor 5-hydroxytryptophan (Meltzer et al. 1984b), and the 5-HT precursor L-tryptophan (Heninger et al. 1984; Cowen and Charig 1987). Five studies have examined lithium's effects in this paradigm.

Slater et al. (1976) found that lithium treatment for at least 2 weeks increased the prolactin response to fenflura-

mine 60 mg PO in four bipolar patients compared with their own pretreatment baselines, but data for this very small sample were not presented. Muhlbauer and Müller-Oerlinghausen (1982, 1985) studied the cortisol response to fenfluramine in four different groups of subjects: 1) 12 healthy subjects who received no fenfluramine; 2) 11 healthy subjects who received fenfluramine 60 mg PO; 3) 11 euthymic patients (7 pipolar, 4 unipolar) maintained on lithium for a mean 6.3 ± 4.4 years, studied initially without fenfluramine and when with fenfluramine 3 months later; 4) 8 euthymic drug-free patients (4 bipolar, 4 unipolar) who received the fenfluramine test dose. Fenfluramine administration had significant effects only in lithium-treated patients: in this group, the usual late-morning decline of plasma cortisol was reversed by fenfluramine, suggesting an enhancement of fenfluramine's effects by maintenance lithium treatment. Meltzer et al. (1984c) found that the cortisol response to 200 mg PO of 5-hydroxytryptophan was increased in seven manic patients tested before and after a mean 24 ± 8 days of lithium treatment. Glue et al. (1986) gave L-tryptophan in a dose of 100 mg/kg IV to eight healthy males pretreatment, after short-term lithium treatment (4 days), and after long-term lithium (20 days) ($n = 7$). The prolactin response was increased to an equivalent degree after both short- and long-term lithium compared to pretreatment. Price et al. (1989) reported that, compared to pretreatment, the prolactin response to L-tryptophan 7 g IV was significantly enhanced in 13 affective disorder patients after short-term (≤ 1 week) lithium treatment, whereas no effect was observed in 13 affective disorder patients after long-term (≥ 3 weeks) treatment.

Miscellaneous studies. Linnoila et al. (1984) reported that "steady-state" lithium treatment reduced urinary 5-HT and 5-HIAA output and "stabilized" (i.e., reduced the variance in) urinary 5-HT output in seven affective disorder patients compared to pretreatment levels. This group also found that 1 week of lithium treatment had no effect on urinary 5-HT and 5-HIAA excretion in 12 healthy control subjects (Rudorfer et al. 1985). However, the significance of these findings is limited by the poor correlation between urinary and brain measures of 5-HT function. Leighton et al. (1983) measured plasma amino acid levels in 12 drug-free and 14 lithium-treated bipolar patients. After 90 days of lithium, there were statistically significant and moderate decreases in levels of isoleucine, leucine, and valine, with significant but smaller decreases in lysine levels after 150 days. Although tryptophan levels were unchanged, the authors suggested that the reductions observed in the other amino acids could result in enhanced tryptophan influx into the brain via decreased competition at the large neutral amino acid uptake mechanism. This possibility is intriguing in light of evidence from some studies that plasma free tryptophan is decreased in depressed patients (Meltzer and Lowy 1987) and that experimentally-induced tryptophan depletion can cause a return of depressive symptoms in remitted depressed patients (Delgado et al. 1988).

Summary. Elucidation of lithium's effects on 5-HT function in humans has been limited by the difficulties inherent in studying central neurobiological mechanisms in humans. Most studies suggest that lithium 1) increases CSF 5-HIAA, 2) increases platelet 5-HT uptake, and 3) increases the neuroendocrine response to 5-HT agonists. Other studies, involving effects on peripheral 5-HT-related receptors, urinary metabolites, and plasma amino acid levels, are too few in number, too contradictory, or too functionally ambiguous to permit much generalization. While available findings are consistent with a net enhancing effect of lithium on 5-HT function, they are insufficiently specific to clarify what mechanisms might underlie such an effect.

Conclusion

This review supports the position of a number of authors who have recently asserted that lithium tends to cause a net enhancement of 5-HT function (Müller-Oerlinghausen 1985; Bunney and Garland-Bunney 1987; Waldmeier 1987; Wood and Goodwin 1987). Studies in humans confirm the existence of the effect, while studies in animals suggest that it results from the complex interaction of a large number of homeostatically regulated processes, rather than as a result of a powerful unidirectional effect at some hypothetical "critical" point. Since most investigators agree that 5-HT function is abnormal in affective disorders (Coppen 1967; Prange et al. 1974; Goodwin and Post 1983; Meltzer and Lowy 1987), with somewhat stronger evidence for diminished function in depression, lithium's effects on 5-HT function seem consistent with its therapeutic efficacy in these disorders.

However, beyond the usual caveats in extrapolating from animal findings to human neurobiology, some evidence suggests that additional caution is warranted in using such findings as the basis for inferences about the interaction of lithium with the pathophysiology of affective disorders. Several studies reviewed above suggest that lithium's effects on 5-HT function differ even between affective disorder patients and healthy subjects (Linnoila et al. 1984; Rudorfer et al. 1985; Glue et al. 1986; Price et al. 1989), and such differential effects may extend to other monoamine (Rudorfer et al. 1985) and neuroendocrine (Grof et al. 1985) systems as well. Some studies show effects of lithium in patients but not in controls, whereas other studies show the reverse. Rather than simply increasing 5-HT function in a deficit state, lithium may help to stabilize (Linnoila et al. 1984) homeostatic systems that are "dysregulated" in affective disorder patients (Siever and Davis 1985). Alternatively, lithium may act on specific processes to help disrupt pathologically "hyperregulated" homeostatic systems (Price et al. 1989). For example, it has been suggested that lithium's ability to enhance presynaptic 5-HT function might interact with postsynaptic 5-HT receptors sensitized by long-term tricyclic antidepressant treatment, resulting in greater clinical improvement than would be obtained with either drug alone (deMontigny et al. 1983; Heninger et al. 1983).

In addition to its effects on 5-HT, lithium has been shown to alter other neurotransmitter systems (e.g., norepinephrine, dopamine, acetylcholine, endorphins, GABA, substance P), cellular ion transport mechanisms, and second-messenger processes (Bunney and Garland-Bunney 1987; Waldmeier 1987; Wood and Goodwin 1987). Which of these actions are primary rather than secondary, and which are related to lithium's clinical effects, are questions for further research. In particular, while this review has considered lithium's neurobiological actions from the perspective of depression, it may well be that non-5-HT mechanisms are more important in mediating lithium's antimanic

effects (Waldmeier 1987). Answers to these questions could lead to a more pharmacologically strategic use of lithium, as well as to insights into the pathophysiological processes lithium is used to correct.

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