The Effects of Lithium Therapy on Thyroid and Thyrotropin-Releasing Hormone

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ABSTRACT

Lithium is used in the prophylaxis of bipolar depressive disorder in augmentation treatment of depression and in the therapy of some cases of unipolar depression. Lithium affects cell function via its inhibitory action on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP), and intracellular enzymes. The inhibitory effect of lithium on inositol phospholipid metabolism affects signal transduction and may account for part of the action of the cation in manic depression. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis. Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake. It also inhibits iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion. The latter effect is critical to the development of hypothyroidism and goiter. Effects on brain deiodinase enzymes and alterations in thyroid hormone receptor concentration in the hypothalamus are under investigation in relation to the therapeutic effect of lithium. The ion affects many aspects of cellular and humoral immunity in vitro and in vivo. This accounts for a rise in antithyroid antibody titer in patients having these antibodies before lithium administration whereas there is no induction of thyroid antibody synthesis de novo. Goiter, due to increased thyrotropin (TSH) after inhibition of thyroid hormone release, occurs at various reported incidence rates from 0%-60% and is smooth and nontender. Subclinical and clinical hypothyroidism due to lithium is usually associated with circulating anti-thyroid peroxidase (TPO) antibodies but may occur in their absence. Iodine exposure, dietary goitrogens, and immunogenetic background may all contribute to the occurrence of goiter and hypothyroidism during long-term lithium therapy. It is currently unclear whether the reported association of lithium therapy and hyperthyroidism are causal, although there is suggestive epidemiological evidence. Finally, lithium therapy is associated with exaggerated response of both TSH and prolactin to TRH in 50%-100% of patients, although basal levels are not usually high. It is probable that the hypothalamic pituitary axis adjusts to a new setting in patients receiving lithium.

INTRODUCTION

THE MAIN USE OF LITHIUM IN THERAPEUTICS is in the treatment and prophylaxis of manic depressive psychosis. In 1949, J.F.J. Cade, an Australian psychiatrist, noticed that guinea pigs that had been given lithium urate during an investigation into the role of uric acid in manic patients became less startled (1). This led to the trial administration of lithium to manic depressive patients, and then to the widely acclaimed studies of Schou and colleagues (2) which defined the clinical effectiveness of this ion in psychiatry. In 1967 the occurrence of goiter in patients receiving lithium was mentioned at a conference in Denmark and these data were reported in 1968 by Schou (3) and others. Since then, a large number of clinical and experimental studies on the effect of lithium on thyroid physiology have been performed and reviewed (4-6). This article briefly reviews lithium effect on cellular metabolism prior to describing its effects on thyroid pathophysiology and thyrotropin-releasing hormone (TRH).

LITHIUM AND CELL FUNCTION

Lithium has many actions on the cell including effects on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP) activity, intracellular enzymes, inositol phospholipid metabolism, and on cell
growth. The inhibitory effect of lithium on inositol phospholipid metabolism is mainly mediated by the ability of the cation to competitively inhibit the enzyme inositol (1,4) P2 1-phosphatase (7). This results in alteration of many intracellular inositol metabolites, thus affecting signal transduction. Intense interest in this action of lithium has occurred and it is thought that its action on these pathways may account for the therapeutic effect in manic depression. Lithium exerts significant effects on inositol lipid metabolism in cultured GH3 pituitary cells when these are exposed to lithium concentrations seen in treated patients (8). Treatment of GH3 cells with 1 mM lithium for 7 days reduces basal and TRH-stimulated levels of inositol 1,4,5-trisphosphate, and this is associated with a reduction in the number of cells showing basal calcium oscillations (9). The precise relation between intracellular calcium secretion, lithium, and inositol metabolism is complex and still unclear. Lithium induces end organ resistance to thyrotropin (TSH) in intact cells at least partly due to its inhibition of adenylate cyclase.

Lithium stimulates DNA synthesis in thyroid cells under basal conditions as well as after stimulation by insulin growth factor-1 (IGF-1); this growth stimulation may partly explain the goitrogenic action of lithium (10). The cation may require the activation of a particular genistein sensitive kinase, possibly a tyrosine kinase, to induce cell proliferation in FRTL-5 cells (11). Lithium has also been shown to have effects on G proteins and it may be capable of modulating the function of G(i)-proteins coupled to IGF-1 receptors during the G(1) phase of the FRTL-5 cell cycle (12).

**EFFECT OF LITHIUM ON THYROID PHYSIOLOGY**

Lithium is concentrated by the thyroid (13), but the relation of the thyroidal lithium concentrating mechanism to the iodide concentrating process is not clear. It is concentrated in mouse salivary glands, which also actively concentrate iodide, perhaps suggesting a common pathway. Lithium reduces the radioiodine (131I) uptake into rat thyroid in vivo (14) and in vitro (15) and into mouse salivary gland (16). In human, lithium administration may result in a reduced, as well as an increased thyroidal radioiodine uptake (17). The possible reasons for this are that lithium causes iodide retention and the increase in uptake may also be due to TSH secreted as a result of lithium-induced hypothyroidism. Lithium inhibits the coupling of iodotyrosines to form iodothyronines in rat thyroid homogenates, but although thyroid hormone synthesis may be impaired, total iodination is not reduced (18) and the overall effect is mild. In humans there is no effect of lithium on the perchlorate discharge test, although if the sensitivity of this test is increased by iodide administration positive tests are seen (19). Lithium may alter thyroglobulin structure by affecting protein conformation and function, thereby leading to minor iodotyrosine coupling defects, but no inhibitory effect of lithium has been observed on the biosynthesis or degradation of thyroglobulin in the rat (20). A reduction in 131I release rate has been found in rats given lithium (17) and reduced thyroxine (T4) release was demonstrated in both euthyroid and hyperthyroid patients receiving the drug (14). Animal data suggests that the block may be distal to cAMP formation (21) in addition to the fact that the process of thyroid hormone secretion involves a decrease in colloid droplet formation together with a number of complex steps involving the degradation of thyroglobulin (22). Lithium does alter tubulin polymerization (23), which may account for its inhibitory effect on hormone secretion. The significant decrease in T4 clearance from plasma in patients receiving lithium (24,25) may be due to inhibition of thyroid hormone secretion, thereby inducing a decrease in type 1 5' deiodidase activity. Lithium causes a decrease in T3 deiodination in rat liver and there are significant inhibitory effects of lithium on T4 to triiodothyronine (T3) conversion in mouse neuroblastoma cells, GH3 cells (26), and humans (27). Administration of lithium to rats for 14 days has been shown to affect intracellular metabolism of thyroid hormones in the frontal cortex of the rat by increasing the type II deiodinase and decreasing the type III enzyme (28). This raises the question as to whether the effects of lithium on thyroid hormone metabolism in the central nervous system (CNS) may be involved in the mood-stabilizing effects of the drug similar to data obtained for other psychotropic agents (29). However, it is still not clear whether these changes in deiodinase activity result from a direct action of lithium on the brain or perhaps by a reduction in serum T4 levels leading in turn to a rise in 5' D-II activity. Lithium can result in an increase in nuclear T3 binding in rat cerebral hemisphere and liver (30), perhaps by inducing "cellular hypothyroidism." Repeated lithium treatment increased THRα1 mRNA in rat cortex, decreased THRα1 mRNA in the hypothalamus and had no effect in the cerebellum. It remains to be determined whether the effects observed on thyroid hormone receptor gene expression are related to the therapeutic value of lithium and/or any thyroidal effect (31).

Lithium affects many aspects of both cellular and humoral immunity (32,33). For example, addition of lithium to peripheral human lymphocytes enhanced the response of these cells to mitogens. It also stimulates interleukin-2 and inhibits suppressor T cells as well as increasing the secretion of immunoglobulins IgA, IgG, and IgM. Numerous studies (see ref. 6) have noted a high proportion of patients receiving lithium as having detectable antithyroid antibodies, and lithium therapy is associated with a rise in these titers in patients who have positive antibodies before starting lithium (34). However, in normal control subjects, lithium administration does not cause any development of antithyroid antibodies but does induce a rise in soluble interleukin-2 receptor level (35). Interestingly, thyroid autoimmunity, as evidenced by the presence of thyroid antibodies, may be weakly associated with subtypes of bipolar disorder in which depressive symptoms are prominent (36). Lithium can exert both positive and negative influences on the course of the development of thyroiditis in an animal model (37). It may influence the uptake of thyroglobulin by macrophages and its subsequent presentation to T cells and may stimulate the increased proportion of helper T cells to produce antibody. Overall the experimental and clinical data suggest that lithium does have significant effects on the course of autoimmune thyroid disease.
CLINICAL EFFECTS OF LITHIUM ON THYROID FUNCTION

The calculated incidence of goiter by Schou (3) was 4% per year per 100 patients on continuous lithium, and this was compared with a 1% incidence in the general population of a separate community (Copenhagen). There is considerable variation in the estimates due to the population sample, observer experience, and method of diagnosing goiter. An overall prevalence in 876 patients was 6.1% (38) and 5.6% in 1257 patients (39). Some groups, however, have found no goiter, while others have found incidence rates of 30%, 37%, and 60%, respectively (see refs. 4–6). If imaging techniques such as scintiscanning or ultrasound were used, significant thyroid enlargement was noted after 3 months of lithium treatment when thyroid volume was compared with pretreatment values (40) in normal female volunteers after 28 days of lithium therapy, but not in males (41). Clinically, the goiter is smooth and nontender. It may develop within weeks of starting lithium therapy (14), or months to years of lithium treatment (39). Thyroid enlargement is due to the initial inhibition of thyroid hormone release (see infra) that results in an increase in TSH. The clinical presentation of hypothyroidism in lithium-treated patients is not different from that seen in other forms of hypothyroidism. Subclinical hypothyroidism may also occur and this should be considered in a patient who is not showing a good response to lithium. Symptoms of the condition may appear within weeks of starting lithium but may not occur for many months or even years and may include the unusual or atypical features such as myxedema coma (42). The female to male ratio is about 5:1 with a significantly higher incidence in females, even when compared with the normally expected higher incidence of this condition in the general population (43). In a review of 16 reports totalling 4681 patients, the prevalence of lithium-induced hypothyroidism was 3.4% (range 0% to 23.3%) (6). While elevated TSH concentrations were transitory in most patients, the risk of developing hypothyroidism was higher in women with thyroid antibodies (44). Clearly, the presence of thyroid antibodies is an important determinant of hypothyroidism in lithium-treated patients, although the inhibitory action of the drug on thyroid hormone release may account for those cases of hypothyroidism that recover to the euthyroid state. The prevalence of thyroid antibodies in patients on long-term lithium therapy varies between 10% and 33% (6). It now seems unlikely that lithium can significantly induce the de novo production of thyroid antibodies, but it may be associated with a rise in antibody titer in patients who already are antibody positive at the start of treatment. Iodine and lithium can act synergistically to produce hypothyroidism. Variations in iodine status, dietary goitrogens, immunogenetic make-up, and their interactions during long-term lithium therapy contribute to the variable pattern of expression of hypothyroidism in different ethnic groups and areas (45). Thus, the pathogenesis of lithium-induced hypothyroidism is either autoimmune or by direct action of lithium on hormone secretion leading to goiter and hypothyroidism.

Despite the general suppressive effect of lithium on thyroid function, a significant number of cases (40–50) of hyperthyroidism have been reported. Review of the clinical characteristics of lithium-associated thyrotoxicosis in 24

![FIG. 1. Serum TSH response to 200 µg, intravenous TRH administered at time 0 in 34 male and 39 female patients receiving lithium carbonate. Normal TSH response is shown by area within the heavy black lines. Abnormal responses are seen in 49.3% of patients (see ref. 6). With permission of Springer Verlag.](image-url)
patients showed that it occurred after many years of lithium therapy in most, but not all patients. The etiology of the hyperthyroidism included Graves' disease, toxic nodular goiter and silent thyroiditis. Recently, a case of granulomatous thyroiditis associated with lithium therapy was described (46), and the thyroid histology in another case (47) showed extensive follicular destruction with no lymphocytic infiltration. Lithium might therefore directly damage thyroid cells with consequent release of thyroglobulin and thyroid hormones into the circulation. It is clearly probable that lithium treatment could mask underlying hyperthyroidism by reduction of thyroid hormones such that when lithium is stopped, hyperthyroidism will appear. Whether lithium induces autoimmune hyperthyroidism by producing thyroid stimulating antibodies is not known, and the reported cases have been thought to be random events. However, a recent epidemiological study concluded that long-term lithium therapy is associated with an increased risk of thyrotoxicosis (48). The association of lithium therapy with exophthalmos has been noted (49,50). In a bipolar patient who developed thyrotoxicosis with severe exophthalmos while taking lithium, the eye signs regressed when lithium was discontinued (51).

EFFECT ON THE HYPOTHALAMIC PITUITARY AXIS

Lithium is concentrated in the pituitary gland as well as the hypothalamus and may interfere with cell metabolism in those tissues as a result of this. In cross-sectional studies, there are numerous reports (see ref. 6) showing that lithium therapy prescribed to psychiatric patients results in an exaggerated TSH response to TRH in at least 50% of patients rising to 100% in others (Fig. 1). Approximately 10% of patients so studied will have an elevated basal TSH, and nonmanic patients treated with lithium also have high basal and stimulated TSH levels. Basal prolactin concentrations are not raised in manic and nonmanic patients on lithium, but they do show exaggerated responses to TRH. While these effects may be due to the feedback effect of reduced thyroid hormone levels, the latter are not always low and this explanation may not be valid. The effect of the ion on pituitary thyroid hormone receptors may also be a cause of the observed changes (vide infra). The enhancing effect of lithium on TRH-induced prolactin release may be related to an ability to decrease in some way, the sensitivity of dopamine receptors to stimulation by catecholamines, but there are no firm experimental data to support this view at present. In a recent longitudinal study in which thyroid function was investigated in 12 euthyemic bipolar patients who had normal thyroid function and negative thyroid antibodies, a significant rise in basal TSH was found in 83% and a rise of TRH-stimulated TSH was observed in 11 after 12 months of therapy. However, the impairment of the hypothalamic (HPA) axis was temporary in most cases. It appears then as if the HPA axis adjusts to a new level of control (or “stat”) during lithium therapy (52).

REFERENCES

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