The Effect of Lithium on Vitamin D Metabolism

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Affective disorders tend to be associated with perturbations in calcium homeostasis, as witnessed in, for example, the major clinical entities of hyper- or hypoparathyroidism (Denko and Koelbing 1962; Hecht and Gershberg 1975). The mood disorders accompanying these diseases are effectively terminated with successful treatment of the underlying endocrinopathy (Anderson 1968; Fourman et al. 1976). In addition, significant shifts in calcium levels in the cerebrospinal fluid (CSF) and serum occur in depressed patients undergoing treatment with electroshock, lithium, or sleep deprivation. Moreover, a positive correlation exists between the severity of the depressive state (bipolar and unipolar) and CSF levels of calcium (Carmen et al. 1977; Gerner et al. 1978; Jimerson et al. 1979).

Lithium, which favorably affects manic and depressive states, acts on a multiplicity of calcium-dependent systems controlling intracellular processes, serving neuronal transmission and transduction by inhibiting or disinhibiting one or another of these systems. For example, lithium inhibits adenylcyclase, tryptophan hydroxylase, inositol-1-phosphatase neurotransmitter release on the one hand, and activates calcium-adenosine triphosphatase (Ca-ATPase) on the other (Meltzer 1986). Lithium increases serum parathyroid hormone (PTH) levels, resulting in a modest elevation of serum calcium and magnesium (Christiansen et al., 1980; Davis et al. 1981).

The purpose of this study was to measure the effects of lithium on the major hormones that are primarily involved in calcium metabolism, namely PTH, calcitonin, and vitamin D. For the latter, the two secosteroids measured were 1,25-dihydroxyvitamin D$_3$ [1,25-(OH)$_2$D$_3$] and 25-hydroxyvitamin D$_3$ (25-OHD$_3$). Ten bipolar or unipolar patients (6 men and 4 women) whose ages ranged between 35 and 60 years, were started on lithium carbonate during a normothymic period. All were completely drug-free for at least 2 months following a depression and were started on prophylactic lithium therapy. Lithium carbonate intake ranged between 900 mg and 1200 mg daily and serum lithium levels varied between 0.6 and 0.8 mEq/liter at 4 weeks. Blood samples taken immediately prior to lithium administration were centrifuged, and the serum was stored on dry ice. After 4 weeks on lithium alone, serum was again collected, frozen on dry ice, and sent, together with the original serum, to the Nichols Institute Reference Laboratories, San Juan Capistrano, CA, for analysis of PTH, calcitonin, 1,25-(OH)$_2$D$_3$, 25-OHD$_3$ and calcium (Holick and Potts 1980; Malette et al. 1982; Segre 1983; Nichols Institute 1983; Teinhardt et al. 1984; Toverud et al. 1986).

As seen in Figure 1, PTH was elevated, and 1,25-(OH)$_2$D$_3$ was reduced ($p < 0.025$ and $p < 0.01$, respectively by Wilcoxin signed-rank test). No significant changes were found for calcium, calcitonin, or 25-OHD$_3$.

The renal enzyme 25-OHD$_3$-l-alpha-hydroxylase, present in proximal convoluted tubules, synthesizes 1,25-(OH)$_2$D$_3$, which is the most po-
Figure 1. Action of lithium on serum levels of parathyroid hormone (PTH) and the secosteroid 1,25-dihydroxyvitamin D₃ [1,25-(OH)₂D₃].

Although lithium decreases the formation of cAMP via inhibition of adenylcylase in some tissues, it fails to inhibit PTH-mediated urinary cyclic adenosine monophosphate (cAMP) (Speigel et al. 1976). Therefore, lithium may act distal to cAMP formation and more immediate to the activation of the hydroxylase to inhibit synthesis of 1,25-(OH)₂D₃. Although the action of 1,25-(OH)₂D₃ on the central nervous system (CNS) is undetermined at this time, there is a high concentration of specific cytosolic receptors for this secosteroid in limbic neurons, particularly in the nucleus centralis of the amygdala and the bed nucleus of the stria terminalis. Smaller concentrations of these receptors are found in the pars distalis of the pituitary, the infundibulum, thalamus, medulla oblongata, and area postrema nucleus tractus salitari (Stumpf et al. 1982).

In the intestine, 1,25-(OH)₂D₃ increases the synthesis of vitamin D-dependent calcium binding protein (CaBP). This occurs via interaction with specific cytosolic receptors that mediate the translocation of the vitamin metabolite to nuclear chromatin, leading to an increased formation of messenger RNA for vitamin D-dependent CaBP (Armbach et al. 1985). Brain CaBP is biochemically and immunocytochemically similar to intestinal vitamin D-dependent CaBP (Feldman and Christakos 1983), but it is not known whether or not brain vitamin D-dependent CaBP synthesis is stimulated by 1,25-(OH)₂D₃.

Clinically, the action of vitamin D on the brain is seen in the reduction of epileptic seizures after vitamin D treatment, without an effect on serum...
calcium and magnesium levels (Christiansen et al. 1974). However, the role of the limbic system in emotional and vegetative functions suggests a possible correlation of the lithium-induced reduction of 1,25-(OH)2D3 levels with changes in affective states. Additionally, the treatment of seasonal affective disorders (Lewey et al. 1982; Rosenthal et al. 1985) with full-spectrum light may also be linked to vitamin D metabolism.

References


