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Curcumin mitigates lithium-induced thyroid dysfunction by modulating antioxidant status, apoptosis and inflammatory cytokines

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KEYWORDS

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Abstract Lithium is an integral drug used in the management of acute mania, unipolar and bipolar depression and prophylaxis of bipolar disorders. It has also been shown to reduce suicidal risk and short term mortality. Few experimental studies have demonstrated the thyroid toxicity caused by lithium as well as the possible protective effect of curcumin. Twenty four male albino rats were divided into three groups; group I (control group), group II received lithium carbonate daily for 6 weeks and group III received the same dose of lithium carbonate as group II concomitantly with curcumin for 6 weeks. The specimens were prepared for histopathological, immunohistochemical and biochemical examination. Lithium-induced thyroid dysfunction evidenced by the histopathological and immunohistochemical changes represented by detached cells and vacuolated cytoplasm of some follicular cells and highly significant increase in positive immunostained of thyroglobulin and caspase-3 respectively. Moreover, a significant decrease in serum free triiodothyonine (FT3), free thyroxine (FT4) concomitant with significantly increased thyroid stimulating hormone (TSH) and pro-inflammatory cytokines, and thyroid lipid peroxidation (MDA) and nitric oxide (NO) levels. Curcumin counteracted lithium-induced oxidative stress and inflammation as assessed by restoration of the antioxidant defenses and diminishing of pro-inflammatory cytokines and improvements in the degenerative changes of the thyroid gland. In conclusion, the present study provides evidence that curcumin exerts thyroprotective effects against lithium carbonate mediated by its antioxidant, anti-inflammatory and anti-apoptotic effect as indicated by caspase-3. This report also confers that the use of this drug should be justified for long treatment under direct medical supervision.

Introduction

Lithium (Li), a psychomodulating drug, was noted to act as a hematopoietic stimulant (Focosi et al., 2009). It is used as a mood stabilizing drug. They have a potential role in the treat-

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ment of depression and mania in both acute and long term conditions (Kalantari et al., 2015). It prevents mood swings in patients with manic-depressive disorder (Bertram, 2001). International multi-center studies yield strong evidence that mortality and suicide rates could be lowered by long-term Li treatment (Niethammer and Ford, 2007). It is a double edged sword; it is a unique drug with an invaluable psychoactive potential on one hand and a drug which can cause multisystem toxicity and even death on the other hand (Kumarguru et al., 2013).

The thyroid gland is the most important endocrine gland for metabolic regulation (Cunningham, 2002). Previous studies reported the thyroid disturbances and dysfunction during lithium treatment, but it rarely-induced parathyroid dysfunction (Nair et al., 2013). Li interference with thyroid functions mainly at the level of hormonal secretion and may result in goitrogenesis, hypothyroidism, or rarely thyrotoxicosis (hyperthyroidism). The inhibitory effect of Li on thyroid hormone secretion has been used in treatment of thyrotoxicosis in selected situations. Treatment with lithium is also accompanied rarely by thyrotoxicosis, where it is not common and occurs mainly after long-term use. The mechanism is unclear but is believed to involve either autoimmune or destructive thyroiditis. Transient euthyroid hyperthyroxinemia has been previously reported after discontinuation of Li treatment (George and Joshi, 2007).

El-bakary and Soliman (2009) reported that lithium carbonate induced severe histological changes in the thyroid gland of albino rat. *In vitro*, Li decreases the formation of colloid droplets within thyroid follicular cells, a reflection of decreased pinocytosis of colloid from the follicular lumen (Williams et al., 1971). Within phagolysosomes, the efficiency of proteolytic digestion of thyroglobulin may also be impaired.

Curcumin (diferuloylmethane), a polyphenol compound, is an active ingredient of tumeric (*Curcuma longa*). Importantly, curcumin has chemopreventive properties and is a safe compound for both humans and animals (Sharma et al., 2005). Moreover, curcumin showed beneficial effects in many cancers including colorectal cancer, breast cancer, skin cancer, and oral cancer (Sa and Das, 2008). It is also used in Asian and African traditional medicine to treat several mild or moderate human diseases such as affections of the pulmonary and gastrointestinal systems; aches; wounds; sprains; and liver disorders (Jurenka, 2009). In addition, a growing body of evidence has unraveled the powerful antioxidant, anti-inflammatory, anticancer and other activities of curcumin depend on the ability of this compound to regulate a number of cellular signal transduction pathways (Shanmugam et al., 2011; Shehzad et al., 2011).

However, there have been few reports describing the histopathological, immunohistochemical and biochemical alterations of the thyroid gland treated by lithium carbonate as well as the protective effect of curcumin and since Li is still a fundamental and widely used drug in psychiatry and Internal Medicine. The present study aims to investigate the effect of lithium carbonate on the thyroid gland of albino rat and the possible protective effect of curcumin through histopathological, immunohistochemical and biochemical studies.

Materials and methods

Drugs and chemicals

Lithium carbonate (Prianil CR)

Lithium was obtained from the Nile Company for Pharmaceuticals and Chemical industries (Cairo, Egypt). It is available in the form of tablets, each one containing 400 mg of lithium carbonate. Curcumin was obtained from Merk Company (Germany).

Animals and experimental design

Twenty four male adult albino rats (*Rattus norvegicus*), weighing about 140–180 g, were used in the current study. All the animals were maintained under standard laboratory conditions of temperature (25 °C) and 12 h light and 12 h dark cycles throughout the experimental period. They were housed in standard cages and had free access to water *ad libitum* and standard diet at the research center in Beni-Suef University. Experiments were conducted as per the guidelines of Institutional Animal Ethical Committee, Beni-Suef University. The animals were divided into three groups (8 each) as follows:

Group I (negative control group)

Included 8 rats being kept without any treatment.

Group II

Included 8 rats, each received lithium carbonate (Prianil CR) at a daily dose of 14.4 mg/kg b.wt/day according to El-bakary and Soliman (2009) for 6 weeks. The drug was dissolved in distilled water then the calculated dose was given orally using gastric intubation.

Group III

Included 8 rats, each received the dose of Li carbonate as group II for the same period and concomitantly with curcumin (60 mg/kg b. wt/day dissolved in distilled water; Sharma et al., 2006) orally by gastric intubation.

Body weight gain was calculated from the difference between the initial weight at the beginning and the final weight at the end of the experiment. To reduce the error originating from feeding, all experimental animals were fasted (water was not restricted) for 10 h before recoding weight.

Samples collection and preparation

At the end of the six weeks of treatment, rats of different groups were killed under light diethyl ether anesthesia. Blood samples, collected from each rat, were allowed to coagulate at room temperature and centrifuged at 1000×*g* for 15 min to separate serum. The sera were quickly removed and kept at −20 °C as aliquots for subsequent biochemical assays. Immediately after sacrifice, thyroid glands from each rat were quickly excised and divided into three portions. One portion was homogenized (10% w/v in cold phosphate buffered saline [PBS]) using a Teflon homogenizer (Glas-Col, Terre Haute, IN, USA). The homogenate was centrifuged at 1000 g for 10 min at 4 °C and the clear supernatant was stored at