Lithium inhibits carcinoid cell growth in vitro.

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Abstract

Carcinoids are slow growing neuroendocrine tumors that often cause debilitating symptoms due to excessive secretion of hormones such as serotonin. Surgery is the only potentially curative treatment, but many patients have unresectable metastatic disease. Lithium is a non-competitive inhibitor of GSK-3 with an established safety profile. The objective of this study was to investigate the effects of lithium on carcinoid cell growth in vitro. Lithium treatment caused a dose-dependent reduction in carcinoid cancer cell (BON and H727) growth. Western blot analysis revealed increased expression of cleaved poly (ADP-ribose) polymerase (PARP), indicating the induction of apoptosis. Lithium treatment also suppressed cellular levels of serotonin and chromogranin A. In summary, lithium inactivates GSK-3, induces apoptosis, and suppresses carcinoid cancer cell growth in vitro. The drug has been used clinically since the 19th century to treat a variety of diseases including bipolar disorder, and its safety profile is well documented. Therefore, based on these findings, we have undertaken a clinical trial of lithium chloride in the treatment of patients with unresectable carcinoid cancer.

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Combination therapy with histone deacetylase inhibitors and lithium chloride: a novel treatment for carcinoid tumors.

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Abstract

In carcinoid cell lines, the histone deacetylase (HDAC) inhibitors valproic acid (VPA) and suberoyl bis-hydroxamic acid (SBHA) activate the Notch1 pathway, whereas lithium inhibits glycogen synthase kinase-3beta (GSK-3beta). These compounds limit growth and decrease hormonal secretion in vitro. We hypothesized that lower-dose combination therapy of HDAC inhibitors and lithium chloride could achieve similar growth inhibition to that of the drugs alone. Gastrointestinal and pulmonary carcinoid cells were treated with either VPA or SBHA and lithium chloride for up to 48 hours. Western blot analysis was used to measure the effects on the Notch1 and GSK-3beta pathways and the neuroendocrine tumor marker chromogranin A (CgA). Growth was measured by a cellular proliferation assay. With lower-dose combination therapy, a decrease in CgA was observed. The HDAC inhibitors increased the amount of active Notch1 protein, whereas treatment with lithium was associated with inhibition of GSK-3beta. Moreover, growth was inhibited with lower-dose combination therapy. Treatment of carcinoid cells with either VPA or SBHA and lithium chloride suppresses the neuroendocrine marker CgA while upregulating Notch1 and inhibiting GSK-3beta. This combination effectively reduces growth. Thus, lower-dose combination therapy may be a viable therapeutic approach for carcinoid tumors.

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