

clusion is provided by reported neurotoxic interactions between lithium and electroconvulsive therapy (ECT) (Small et al. 1980) that might be related to a combination of ECT-induced cholinergic effects with those of lithium.

It would thus seem premature to link the mood-stabilizing effect of lithium to a stabilizing effect of the ion on muscarinic receptors. Present evidence suggests that on the receptor binding level, this finding is controversial, whereas on the functional level, lithium appears to increase rather than attenuate cholinergically mediated effects.

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Response

To the Editor:

In a recent article, I hypothesized that lithium ion diminishes the propensity of cholinergic systems to undergo up-regulation and supersensitization consequent to exogenous and endogenous events apt to induce these states (Dilsaver 1984; Dilsaver and Greden 1984). Drs. Lerer and Stanley take issue with this. However, I suggest that their arguments are flawed. I will discuss these within the context of my article. My first concern is the manner in which Drs. Lerer and Stanley use evidence. A focus of the article was the inconsistency in the literature regarding lithium's effects on muscarinic receptor binding parameters. This extends to reports of other effects of lithium on cholinergic systems. Variability or inconsistency within this literature does not negate a hypothesis. However, it does call attention to the needs to identify confounding variables that may account for

Honchar MP, Olney JW, Sherman WR (1983): Systemic cholinergic agents induce seizures and brain damage in lithium-treated rats. *Science* 220:323-325.

Lerer B, Stanley M (1985): Effect of chronic lithium on cholinergically-mediated responses and (³H)QNB binding in rat brain. *Brain Res* in press.

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Samples J, Janowsky DS, Pechnick R, Judd LL (1977): Lethal effects of physostigmine plus lithium in rats. *Psychopharmacology* 52:307-309.

Small JG, Kellamy JJ, Melstein V (1980): Complications with electroconvulsive treatment combined with lithium. *Biol Psychiatry* 15:103-112.

Staunton DA, Magistretti PJ, Shoemaker WJ, Deyo S, Bloom FE (1982): Effect of chronic lithium treatment on dopamine receptors in the rat corpus striatum. II. No effect on denervation or neuroleptic-induced supersensitivity. *Brain Res* 232:401-412.

these, and then to test hypotheses experimentally while properly controlling for these confounders. Without this, "negative" and "positive" evidence would likely continue to accumulate without provision of a means to arbitrate between them. Drs. Lerer and Stanley focus on "negative" evidence in the literature, that speaking against my hypothesis, despite a considerable body of evidence supporting my viewpoint.

We have a problem with inconsistency in the lithium literature, but a more fundamental question is, "Why this inconsistency?" First, Drs. Lerer and Stanley refer to Samples et al. (1977) as offering data suggesting that lithium potentiates the neurotoxic effects of cholinergic agents. I, too, cited this article, but noted that the investigators used "mega" doses of lithium chloride. The equivalent doses, in milliequivalents

per day, of lithium carbonate for a 70-kg man would have been 11,045 and 22,090 mg daily. This raised the question of lithium toxicity having interfered with the monoaminergic compensatory response to physostigmine-induced cholinergic overdrive (Katz et al. 1968). It is noteworthy that this report comes from the San Diego group of Janowsky, Judd, and colleagues. This group has also reported that lithium antagonizes behavioral effects of cholinergic agents in rodents (Janowsky et al. 1978, 1979, 1982). Hence, the same group reports data capable of supporting contradictory viewpoints. I suggest that rather than focusing on "contradictions," reasons for inconsistencies and the general tenor of the group's findings be emphasized. Given the doses of lithium chloride used, the inconsistency of other reports from the San Diego group and the main current of that group's research in this area, it may be special pleading to use the report by Samples and associates against my hypothesis. Alternatively, the data reported by Samples et al. (1977) must be regarded within its proper context.

Lerer and Stanley also refer to a report by Honchar et al. (1983) that concurrent systemic administration of cholinergic agents and lithium produced synergistic toxic effects on rodent brain. This issue of dose is again relevant. The authors administered 3 meq/kg of Li^+ and followed this with pilocarpine or physostigmine challenge 24 hr later. The typical 70-kg male receiving 600 mg of lithium carbonate b.i.d. receives only 0.46 meq/kg Li^+ daily. Honchar et al. reported that 10 hr after lithium administration, animals had a mean plasma Li^+ level of 0.69 meq/liter. However, this does not allow us to predict peak Li^+ levels and to rule out the possibility of high levels soon after administration having had long-lasting effects on neural function. After all, lithium is a neurotoxic agent.

Lithium is associated with muscarinic and nicotinic cholinergic receptor down-regulation. Levy et al. (1982) reported that chronic lithium treatment prevented atropine-induced muscarinic receptor up-regulation in rats. Pestronk and Drachman (1980) reported that lithium reduced the density of extrajunctional nicotinic acetyl-

choline receptors in denervated skeletal muscle. In each instance, down-regulation of cholinergic receptors occurred in association with a manipulation apt to produce receptor up-regulation. This may be the most effective, if not an essential, means of demonstrating the capacity of lithium ion to prevent up-regulation of cholinergic receptors. There is good evidence for lithium ion acting on cholinergic receptors in the manner I hypothesized, but there is also a need for more research in this area.

Drs. Lerer and Stanley subtly implied that lithium's inability to prevent the antipsychotic-induced up-regulation of dopamine receptors impugns the hypothesis that it prevents up-regulation or supersensitization of cholinergic receptors. If this is intended, it is a type of "category error." Dopaminergic and muscarinic receptors are within different epistemic categories, and general or particular statements pertaining to one of these categories need not pertain to the other.

Drs. Lerer and Stanley found that scopolamine pretreatment enhanced cholinomimetic-induced hypothermia and catalepsy. This is predicted by the extant literature (Dilsaver 1985). They also report that scopolamine pretreatment produced muscarinic receptor up-regulation in the cortex, hippocampus, and striatum, that pretreatment with lithium alone was associated with an increased density of [^3H]QNB binding sites in cortex, and that combined pretreatment with lithium and scopolamine had an additive effect. Drs. Lerer and Stanley present these points as arguing against the hypothesis set forth. However, I cannot properly comment on them or interpret their meaning vis-à-vis my article without first knowing their experimental methods and examining their raw data. Incidentally, this critical approach to the lithium literature was that which I was advocating as essential to producing order in an otherwise chaotic sphere.

Lerer and Stanley's letter calls attention to inconsistencies and problems in the lithium literature. There are means for dealing with these difficulties and introducing more order into this area. Problems present opportunity! Problems addressed by the article and this letter point to

a basic tenet of scientific inquiry. Researchers routinely assume the validity of hypotheses for operational purposes. Ascription of "validity" does not mean one believes a hypothesis to be "true." One may or may not. The issue is sincerity or genuineness of intent. Regardless of one's belief, assumption of the validity of a hypothesis promotes sincere examination of it. Thus, ascription of "truth" to a hypothesis is an epistemic driving force when it encourages sincere inquiry. This is the attitude with which I presented the hypothesis that lithium diminishes the propensity of cholinergic systems to undergo up-regulation and supersensitization consequent to exogenous and endogenous events apt to induce these states. I presented it so that it would receive attention and receive systematic study and, in so doing, intended it to be judged on the basis of its heuristic value. It is here that it is best understood. After accounting for a plethora of data and identifying sources of variance in the lithium literature, I concluded that this hypothesis has utility and is of heuristic value. It may or may not be "true," but if it encourages fruitful study, it will have served its purpose. We currently lack the knowledge justifying closure on this subject, and inconsistencies in the lithium literature only draw attention to the need for more research on this potentially rewarding topic.

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