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Effects of Haloperidol, Lithium, and Valproate on Phosphoinositide Turnover in Rat Brain

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LI, R., L. L. WING, R. J. WYATT AND D. G. KIRCH. *Effects of haloperidol, lithium, and valproate on phosphoinositide turnover in rat brain.* PHARMACOL BIOCHEM BEHAV 46(2) 323-329, 1993.—The effects of acute, subacute, and chronic treatment with haloperidol, lithium, and valproate on inositol phosphate (IP) formation were examined. Acute treatment with haloperidol or the combination of haloperidol and lithium significantly reduced IP basal cortical levels. Subacute (three days) treatment with lithium decreased the IP basal level in the frontal cortex. Chronic treatment with haloperidol (14 and 28 days) caused a significant attenuation of carbachol-sensitive IP accumulation in the frontal cortex and striatum and a significant decrease in norepinephrine (NE)-induced IP formation in the frontal cortex (14 and 28 days) and striatum (28 days). Lithium treatment for 14 days produced a significant reduction in the IP basal cortical value, and a significant reduction in cortical carbachol- and NE-induced IP formation was found after 28 days of lithium treatment. The combination of haloperidol and lithium for 28 days decreased the striatal carbachol- and cortical NE-induced IP accumulation and caused a significant increase in NE-sensitive IP formation in the striatum at 14 days. Valproate treatment for 28 days was associated with a significant attenuation in striatal agonist-stimulated IP formation. Therefore, three drugs with different specificities for primary neurotransmitters may have common effects on second-messenger systems.

Haloperidol Lithium Valproate Inositol phosphates Frontal cortex Striatum

OVER the last several decades, the treatment of mania in patients with bipolar disorder has advanced significantly. First with the introduction of neuroleptic drugs such as haloperidol, and subsequently with the use of lithium salts, effective drug treatments for manic episodes became widely available (18). Recently, a growing literature indicates that the anticonvulsant medication, valproate, may also be effective in the treatment of bipolar disorder (7,8,13,29). While these medications appear to treat the same syndrome, it is not clear whether they work through a common pathway. It has been demonstrated that neuroleptics, lithium, and valproate differ in terms of their effects on brain neurotransmitter systems. For example, haloperidol is proposed to have its clinical efficacy via the blockade of central nervous system (CNS) dopaminergic receptors (38), while valproate increases gamma-aminobutyric acid (GABA) levels in various brain regions via inhibition of GABA catabolism and activation of GABA synthesis (10,33). Lithium has effects on multiple neurotransmitters, increasing GABA, serotonin (5-HT), and dopamine (36). Given that three drugs with such different effects on CNS neurotransmitters have all been shown to have antimanic efficacy, the question arises as to what common mechanism might underlie this effect.

It has been demonstrated that lithium, the standard treatment for bipolar disorder, alters the turnover of phosphoinositide (PI) in the intracellular second messenger system (3,5,31). In an earlier study, we found that 6 weeks of treatment with haloperidol also produced a decrease in agonist-stimulated inositol phosphate (IP) accumulation in the rat brain (24). This, in turn, raises the possibility that the different primary effects of these drugs on neurotransmitter systems (first messengers) might converge in a common mechanism of action, for example, a similar modulation of the second-messenger system. In the present study, we investigated the effects of acute, subacute, and chronic administration of three antimanic drugs, haloperidol, lithium and valproate, on basal and agonist-stimulated formation of IP in rat frontal cortex and striatum slices.

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METHOD

Animals and Treatments

Male Sprague-Dawley rats (Zivic Miller, Allison Park, PA), weighing 230–250 g, were housed in groups of three per cage in a temperature-controlled environment (24 ± 1°C) with alternating 12 L : 12 D cycles. The rats were allowed free access to food and water at all times. The study was comprised of four different treatment periods: a single acute dose, subacute treatment for three days, and two chronic treatment periods of 14 and 28 days, respectively.

To choose a time point for sacrifice after acute drug administration, we did an initial time-course pilot study of the effects of haloperidol and valproate on PI turnover. Rats were randomly assigned to treatment and control groups (n = 6 per group). Animals in each group received a single injection of haloperidol (1.5 mg/kg) or valproate (200 mg/kg, IP) and were sacrificed after 0.5, 1.0, 2.0, 3.0, or 4.0 h. A group of age-matched control animals (n = 6) received a single injection of saline (0.5 ml, IP). Our results showed that neither haloperidol nor valproate had a significant effect on agonist-stimulated PI turnover over the time course studied (Fig. 1). However, there was a significant decrease in IP_1 basal level and a trend toward increased carbachol-stimulated IP_1 accumulation in those animals who had a single injection of haloperidol 3 h before they were decapitated. It has been shown that the half-life of valproate in plasma, after a single injection of the drug at a dose of 200 mg/kg is 1.6 h. In addition, the drug concentration in plasma reached the highest level within 1 h and declined after that point (25). Therefore, we chose 3 h for the acute haloperidol treatment and 1 h for valproate in the present study. Lithium-treated animals were decapitated 18 h after acute injection, based on results from a previous study, which reported that the peak lithium concentration in the brain is 18–24 h after an injection (31).

In the acute experiment, 30 rats were divided into five groups (6 rats per group). Each of the 5 groups was treated IP with a single dose of one of the following: vehicle (saline or buffer 0.5 ml/animal), valproate (200 mg/kg, Sigma, St. Louis, MO), haloperidol (1.5 mg/kg, LyphoMed Inc., Rosemont, IL), lithium (6.75 mEq/kg, Mallinckrodt Inc., Paris, KY), or a combination of haloperidol (1.5 mg/kg) and lithium (6.75 mEq/kg). As noted above, valproate-treated animals were sacrificed after 1 h, haloperidol-treated animals after 3 h, and lithium-treated animals after 18 h. In the combined treatment group, lithium was injected first and haloperidol 15 h later, and these animals were decapitated 3 h after haloperidol administration.

In the subacute experiment, 5 groups of rats (six rats per group) were injected intraperitoneally daily for 3 days with the same doses of vehicle, valproate, and haloperidol described above. The lithium dose (2.5 mEq/kg/day), however, was lower than in the acute treatment experiment to avoid the toxicity associated with high blood levels.

The chronic experiments involved 14 and 28 days of treatment with vehicle (saline or sesame oil), valproate (200 mg/kg/day, IP), haloperidol-decanoate (21 mg/kg/2 weeks, IM, McNeil Pharmaceutical, Spring House, PA), lithium (2.5 mEq/kg/day, IP), or the combination of haloperidol and lithium (21 mg/kg/2 weeks, IM, and 2.5 mEq/kg/day, IP, respectively).

All animals from the subacute and chronic treatment groups, 6 rats in each treatment group, were sacrificed 24 h after the last daily injection. Haloperidol-decanoate treated rats were decapitated 2 weeks after the last injection of haloperidol. The dose and duration of the treatments were based on various studies (14,21,26,28), which reported that haloperidol in doses of 0.25 to 5 mg/kg, acutely or chronically, can cause significant CNS neurochemical changes. It has been reported that haloperidol decanoate is highly lipophilic and provides virtually 100% bioavailability when administered intramuscularly (20). Because haloperidol decanoate is an ester that is hydrolyzed into haloperidol and decanoic acid, administration of haloperidol decanoate results in slow sustained release of haloperidol. The half-life of a single-dose injection of haloperidol decanoate is 12–16 days and the peak concentration of haloperidol in the frontal cortex and striatum occurs 2 days after the injection and remains high for 7 days (4). In

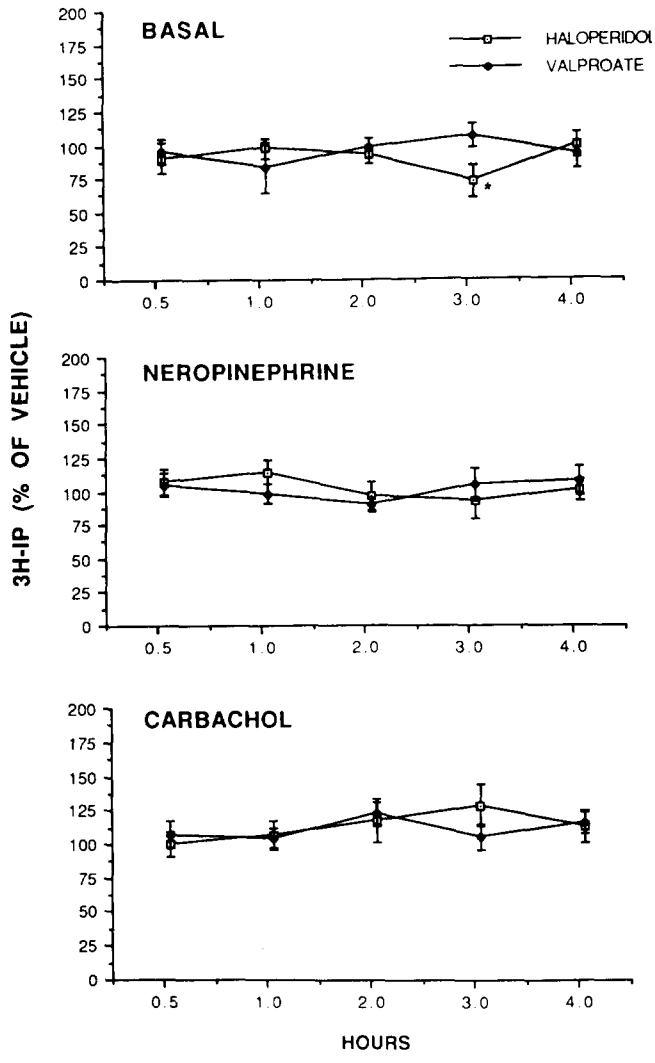

FIG. 1. Time-course effects of a single dose of haloperidol or valproate on PI turnover in frontal cortex slices. Rats received a single-dose injection of haloperidol, valproate, or saline 0.5, 1.0, 2.0, 3.0, or 4.0 h before sacrifice. Each group had five or six rats. The data represent total [^{3}H]-IP_1 formation in the drug treated group expressed as a percentage of the formation in vehicle animals. The basal level of vehicle was 459–512 dpm. The radioactivity of carbachol- or NE-stimulated IP was 956–1197 dpm. The figure represents the mean of two or three independent experiments each done in triplicate. *p < 0.05 compared with vehicle animals.

this study, we opted to use the decanoate form of haloperidol for chronic treatment to decrease the number of injections administered to the animals and thereby decrease the variance. The time of sacrifice for the chronic haloperidol treatment groups was determined by the extended half-life of the decanoate form.

In all experiments the brain was removed rapidly and the frontal cortex and striatum were dissected on ice. Carotid blood was taken from lithium treated animals for determination of lithium levels by flame photometry.

[^{3}H]-IP Formation

Brain slices were prepared by cross-chopping, using a McIlwain tissue chopper set at 0.35 mm. The slices were preincubated in Krebs–Heinslett Buffer (KHB) containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM KH_2PO_4, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 11 mM glucose, and 25 mM $NaHCO_3$. Slices were shaken constantly and gassed with 95%O_2–5%CO_2 for 45 min. at 37°C, and the buffer was replaced once. The slices were then incubated with a fresh buffer containing 0.3 μM myo-[2-^{3}H]inositol (19.9 Ci/mmol, Amersham Corp., Arlington Heights, IL) for 60 min. and washed three times with room temperature KHB. Forty microliters of packed slices were dispersed into polypropylene tubes containing 240 μl KHB and 5 mM LiCl and incubated for 20 min. Then, either 1 mM carbachol, 0.1 mM norepinephrine (NE), or 20 ml of KHB was added to the tubes, and incubated for an additional 45 min. The agonist stimulation was terminated by the addition of 0.9 ml chloroform/methanol (1 : 2, v/v). Further aliquots of chloroform and water were added. Following centrifugation (5000 rpm, 5 min), the supernatants were applied to columns containing 1 ml of Dowex anion exchange resin (AG, 1 × 8 formate form, 100–200 mesh, Biorad Labs., Richmond, CA). Free inositol was eluted with water, and inositol monophosphate (IP_1) was eluted with 0.2 M NH_4CO_2H/0.1 M HCOOH. Radioactivity was counted by a liquid scintillation counter. To measure the incorporation of [^{3}H]inositol into phospholipids, a 200 ml aliquot of the organic phase was air dried and counted.

Statistical Analysis

For each length of treatment, a two-way analysis of variance (ANOVA) was performed on the basal, carbachol-, and NE-stimulated IP data for the five different treatments. Significant differences between treatment groups were analyzed using post-hoc *t*-test comparisons.

RESULTS

Acute Treatment

The effects of a single dose of valproate, haloperidol, lithium, and haloperidol/lithium on agonist-stimulated IP accumulation in frontal cortex and striatum slices are shown in Fig. 2. Cortical and striatal carbachol-stimulated and NE-stimulated IP formation were not affected by acute drug treatment. However, the basal concentrations of [^{3}H]-IP_1 in the frontal cortex were significantly reduced in rats treated with haloperidol alone, or the combination of haloperidol and lithium. A single dose of valproate or lithium had no effect on the [^{3}H]-IP_1 basal levels in either brain region.

Subacute and Chronic Treatment

In the frontal cortex, [^{3}H]-IP_1 basal levels were significantly reduced after 14 days of lithium treatment (Fig. 3). There was a trend toward a significant increase in the basal concentration of [^{3}H]-IP_1 in the frontal cortex in rats treated with valproate for 28 days ($p = 0.064$). No other significant

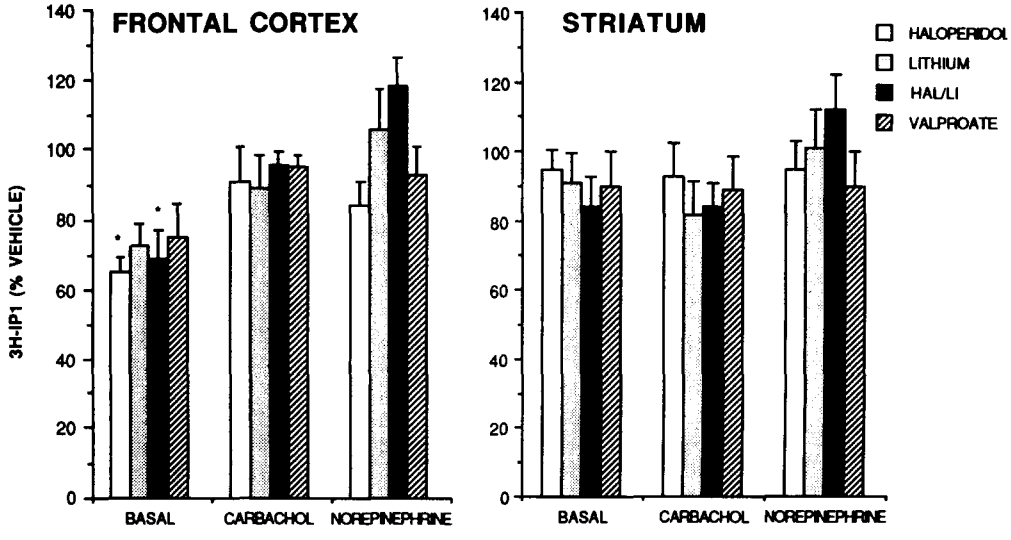

FIG. 2. Effects of acute drug administration on agonist-stimulated [^{3}H]-IP_1 accumulation in rat frontal cortex and striatum slices. Rats were injected with a single-dose of vehicle, haloperidol, lithium, valproate, or a haloperidol/lithium combination. Drug dosage is described in the Methods section. Lithium serum concentration was 0.53 ± 0.12 mM ($n = 8$). The data represent total [^{3}H]-IP_1 accumulation from drug-treated animals expressed as a percentage of the accumulation in the slices from vehicle animals incubated under the same conditions. Cortical and striatal basal radioactivity was 340–550 dpm in the vehicle treated animals. The figure represents the mean of three independent experiments each conducted in triplicate. *$p < 0.05$ compared with vehicle animals.

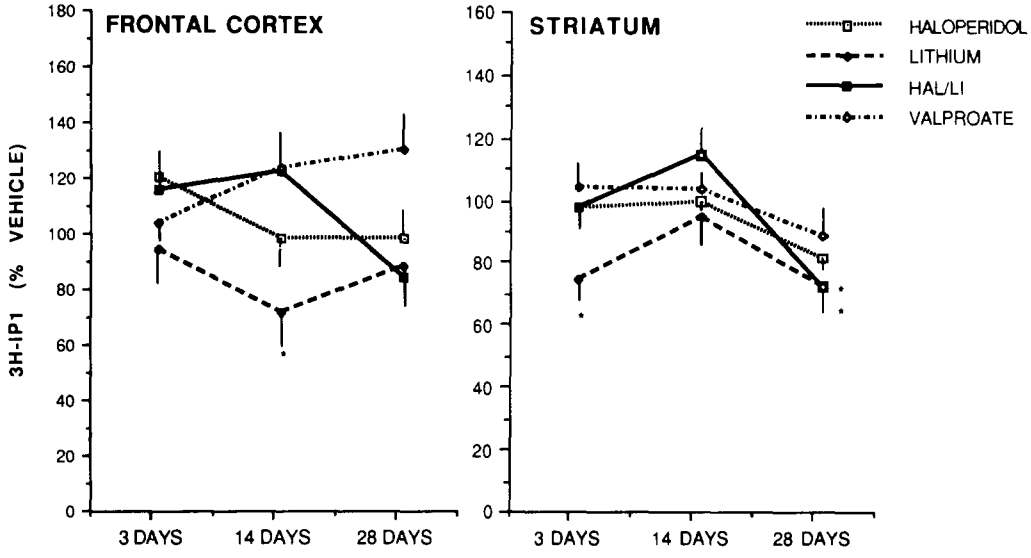

FIG. 3. Effects of subacute and chronic drug treatment on basal concentration of [^{3}H]-IP$_1$ in the frontal cortex and striatum. Rats were treated with vehicle, haloperidol, lithium, valproate, or haloperidol/lithium with doses as described under Methods for 3, 14, or 28 days, respectively. Rat brain slices from five different treatments were preincubated with 0.3 μM myo-[2-^{3}H]inositol. Five mM LiCl was then added with a further 45 min. incubation period. The data represent the percentage of [^{3}H]-IP$_1$ concentration compared with vehicle animals (mean ± SEM) from three independent experiments, each done in triplicate. Cortical and striatal basal radioactivity were 330–500 dpm in vehicle treated rats. *$p < 0.05$ compared with vehicle animals.

changes in basal concentrations were observed in the frontal cortex.

Lithium significantly decreased the [^{3}H]-IP$_1$ basal concentration in the striatum in rats treated for 3 days and for 28 days. The [^{3}H]-IP$_1$ basal level in the striatum was also significantly decreased following combined treatment with haloperidol and lithium for 28 days. Valproate and haloperidol alone had no effect on basal [^{3}H]-IP$_1$ levels in the striatum.

Subacute (3 days) injections of valproate, haloperidol, lithium, and haloperidol/lithium had no significant effect on carbachol-stimulated [^{3}H]-IP$_1$ accumulation in the frontal cortex or in the striatum (Fig. 4). The inhibitory effects of haloperidol on carbachol-induced [^{3}H]-IP$_1$ accumulation were significant at 14 days and persisted at 28 days of treatment in both brain regions. Lithium treatment for 28 days resulted in a marked attenuation of carbachol-stimulated [^{3}H]-IP$_1$ accumulation in the frontal cortex and the striatum. Rats treated with haloperidol combined with lithium for 28 days had a significant reduction in carbachol-stimulated [^{3}H]-IP$_1$ formation in the frontal cortex, but the 12% decrease in the striatum was not statistically significant. In the striatum, the accumulation of [^{3}H]-IP$_1$ induced by carbachol was also downregulated significantly with 28 days of valproate administration.

Subacute drug administration for 3 days had no significant effect on NE-induced [^{3}H]-IP$_1$ accumulation in either brain region (Fig. 5). Haloperidol treatment attenuated NE-sensitive [^{3}H]-IP$_1$ accumulation in the frontal cortex at both 14 and 28 days, but only after 28 days in the striatum. Lithium also significantly decreased NE-stimulated [^{3}H]-IP$_1$ accumulation after 28 days, in the frontal cortex, but not in the striatum. Similarly, valproate decreased this accumulation in the striatum but not in the frontal cortex at 28 days. Rats treated with haloperidol combined with lithium for 14 days showed an increase in NE-stimulated accumulation in both the frontal cortex and the striatum, but only the effects in the striatum were significantly different compared with the vehicle animals.

There were no significant differences in striatal or cortical [^{3}H] inositol incorporation associated with total inositol phospholipids following either acute or chronic drug treatment compared with the levels found in vehicle animals.

DISCUSSION

Neurotransmitters and other neuromodulators carry out their physiological roles by stimulating specific receptors on the cell surface. These receptors transduce and amplify extracellular signals through the generation of second messengers such as inositol 1,4,5 trisphosphate (IP$_3$), a second messenger that releases calcium from the endoplasmic reticulum (11). Some receptors have been found to be coupled to phospholipase C, the enzyme that forms IP$_3$ by hydrolyzing phosphoinositide. These receptors include serotonin (5-HT$_{1c}$, 5-HT$_2$), acetylcholine (M$_1$, M$_3$, and M$_5$), and norepinephrine (α_1) (15). In addition, it has been reported that dopaminergic receptors (D$_1$ and D$_2$) regulate PI turnover in the CNS (27,34).

Neurochemical studies of bipolar disorder have indicated possible abnormalities in diverse neurotransmitter systems, including NE, DA, acetylcholine (ACh), 5-HT, and GABA (18). Recently, however, attention has turned toward the role of second-messenger systems in this illness. A number of studies have demonstrated compelling data that lithium significantly downregulates receptor-mediated PI turnover in the CNS (9, 12,22). At therapeutic doses, lithium causes a decrease in the content of myo-inositol in the CNS (1), an observation subsequently found to be associated with inositol phosphatase inhibition (19). While Sherman and colleagues found that acute injection of lithium increased basal [^{3}H]IP$_1$ levels via inhibiting monophosphatase (31), Kendall and associates found a decrease in carbachol-stimulated [^{3}H]IP$_1$ accumulation and no

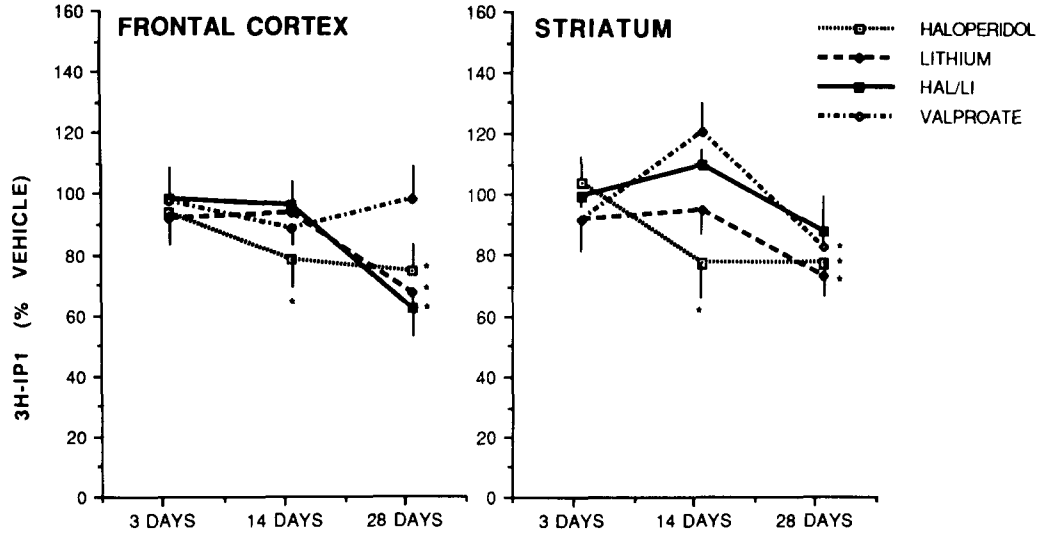

FIG. 4. Effects of subacute and chronic drug treatment on carbachol-stimulated [^{3}H]-IP$_1$ accumulation in the frontal cortex and striatum. [^{3}H]-IP$_1$ accumulation was measured in the presence of 1 mM carbachol. The data shown represent the percentage of [^{3}H]-IP$_1$ concentration compared with vehicle animals (mean ± SEM) from three independent experiments, each done in triplicate. In vehicle-treated animals, carbachol stimulation of [^{3}H]-IP$_1$ was three times that of the basal level. *$p < 0.05$ compared with vehicle animals.

effect on basal or NE-sensitive [^{3}H]IP$_1$ formation in the rat cerebral cortex after a single-dose injection of lithium (22). Godfrey found no change in either basal or agonist-induced [^{3}H]IP$_1$ in the rat brain in response to acute lithium treatment (17).

Our results show that acute treatment with lithium has no significant effect on either basal or agonist-stimulated PI formation in either the frontal cortex or the striatum (Fig. 2). It is possible that the variation of results from these studies may be related to different concentrations of lithium in the serum. For example, in our study, the lithium level in rats treated acutely was between 0.4–0.6 mM, similar to the level used by Godfrey and colleagues (17), but slightly lower than concentrations reported by Sherman and associates (31). In any event, the relationship between lithium serum level and the effect of lithium on PI turnover remains to be conclusively demonstrated.

Our data on the effect of chronic lithium treatment on IP

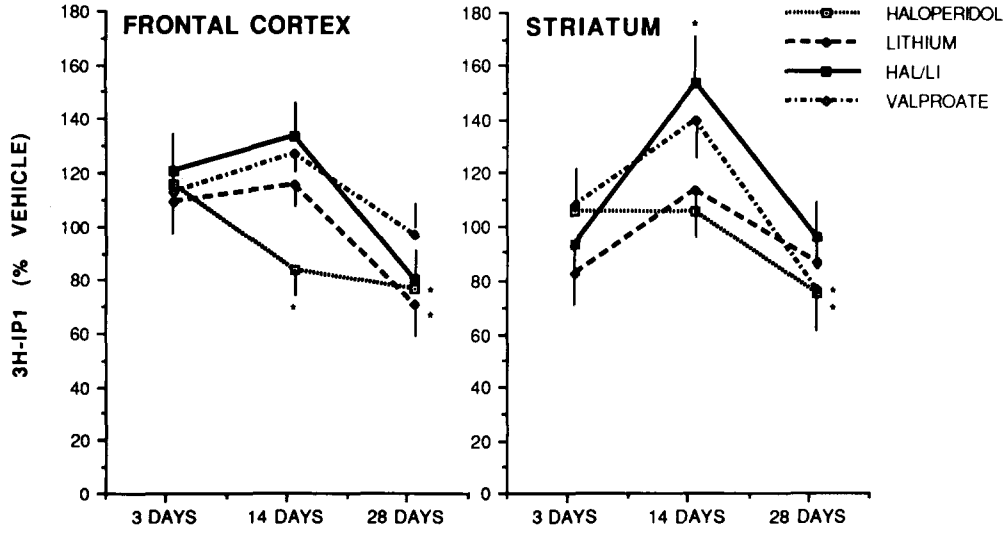

FIG. 5. Effects of subacute and chronic drug treatment on NE-sensitive IP formation. Brain slices from different treatments were prepared and stimulated with NE as described in the Methods section. Concentration of NE was 0.1 mM. The data are expressed as the percentage of [^{3}H]-IP$_1$ accumulation compared with vehicle animals (mean ± SEM) from three separate experiments, each performed in triplicate. In vehicle animals, NE-stimulated [^{3}H]-IP$_1$ was four times that of the basal level. *$p < 0.05$ compared with vehicle animals.

formation are consistent with previous studies (9,22,37). While the effect of chronic lithium on agonist-stimulated IP accumulation has been well studied, its mechanism is still unclear. One possibility is that the inhibition of monophosphatase depletes the inositol pool and slows the PI cycle by preventing the formation of phospholipids and IP3 (3). While our data indicate no significant reduction in the incorporation of [^{3}H]inositol into total phospholipids in the drug-treated rats, we did not measure total phosphoinositides. Another proposed mechanism is that lithium induces changes in the receptor-G-protein-phospholipase C complex (2,30).

The effect of lithium on various aspects of PI turnover suggests that hyperactivity of PI metabolism may be involved in bipolar disorder, although to our knowledge there are no data that directly support such a conclusion. Nevertheless, studying the effects on PI turnover of other drugs which have been clinically demonstrated to have antimanic actions may reveal common mechanisms underlying their therapeutic efficacy. Haloperidol, a neuroleptic drug and potent dopamine receptor antagonist, is effective in the treatment of mania (32). In manic patients with extreme hyperactivity and psychotic features, it is often the most rapid means of controlling symptoms. In the present study, we found that haloperidol attenuated IP accumulation stimulated by carbachol in the frontal cortex and the striatum of rats treated for 14 or 28 days. This finding is consistent with our earlier studies, which showed the same effect in the hippocampus, as well as in the frontal cortex and the striatum, after six weeks of treatment (23,24). These data, which were obtained using biweekly injections of haloperidol decanoate, are also consistent with the effects on IP accumulation we have observed using daily injections of haloperidol (unpublished data). The effect of haloperidol on carbachol-induced IP accumulation may be related to enhanced ACh release, perhaps as a result of desensitization of postsynaptic muscarinic receptors (6,11). Our primary data show that haloperidol did not decrease the synthesis of phospholipids in either the frontal cortex or the striatum. At this point, the mechanism of action of haloperidol on PI turnover remains unclear.

In contrast to the inhibitory effects of haloperidol on receptor-mediated-PI turnover observed in the present study after 14 days of treatment, lithium and valproate inhibited PI turnover only after 28 days of treatment. Further study might address the question of whether the earlier effect of haloperidol on PI turnover corresponds with its more rapid onset of clinical action in mania than the effect observed with lithium.

Chronic treatment with haloperidol also decreased NE-sensitive IP accumulation in the frontal cortex and striatum. The mechanism of this effect is also unknown. However, it is unlikely to be due to a decrease of adrenoceptor binding sites because long-term treatment with haloperidol has been shown to increase the density of α_1-adrenergic receptors in the rat cerebral cortex (26). On the other hand, a significant reduction of the basal IP concentration in the frontal cortex was observed after acute administration with haloperidol.

The combination of a neuroleptic with lithium is also a common treatment approach in an acutely manic patient (16). However, in our study the combination of both drugs had less of an effect on both carbachol- and NE-stimulated IP accumulation in the striatum than either drug alone. In the frontal cortex, the combination showed the same significant inhibitory effect on carbachol-stimulated IP accumulation as haloperidol alone and lithium alone.

Although lithium remains the mainstay of antimanic treatment, a significant proportion of patients with bipolar disorder do not respond to lithium or are unable to tolerate the side effects. Valproate, an anticonvulsant, often provides significant therapeutic benefit for these patients (7,8). The present data indicate that chronic valproate treatment significantly reduced carbachol- and NE-sensitive IP formation in the striatum. Thus, valproate had a similar inhibitory effect on receptor-mediated PI turnover to that observed with lithium and haloperidol.

The mechanism underlying this effect of valproate on PI turnover is not known. A study by Vayer and colleagues indicated that gamma-hydroxybutyrate (GHB), a GABA metabolite, increases cAMP and IP levels in the CNS and this action can be blocked by valproate (35). The density of GHB receptors is high in rat whole brain synaptosomal fractions and low in the frontal cortex, where we failed to see any effect of valproate on PI turnover. However, it seems unlikely that the effects of valproate on the PI signaling system were mediated directly by GABA receptors since no changes in basal IP concentrations in valproate treated animals were found in the present study.

In summary, our data indicate that chronic treatment (14 and/or 28 days) with haloperidol, lithium, or valproate results in a modest but statistically significant downregulation of receptor-mediated PI turnover in some rat brain regions. It remains to be determined whether the common actions of these drugs on PI turnover, after chronic administration, may be an important factor underlying the common clinical efficacy of all three drugs in treating mania. In general, the study of the effects of psychopharmacological agents on second-messenger systems may be important in elucidating how drugs with widely differing specificities for neurotransmitter receptors may all be effective in treating a given mental disorder.

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