ferential sensitivity of primary and secondary EP components to exogenous and endogenous processes, respectively, these data are presented as four sequences of differences between estimates of the magnitudes of exogenous and endogenous representations (Fig. 3). If the influences of these two classes of process on the average EP components were not differential, the difference between coefficients should vary randomly about zero. However, if the influences are differential, the particular sensitivity of a component would be manifested in a systematic and nonzero difference; the magnitude of the difference reflects how selectively the average EP components reflect exogenous and endogenous influence, and the sign corresponds to the particular sensitivity.

The primary component of the EP appears particularly sensitive to exogenous representational processes (Fig. 3, A and B), whereas the secondary components tend to reflect endogenous processes (Fig. 3, C and D). Dynamic changes in the manifestation of these representations with the cat's movement relative to the cue source and with phases of cognitive-behavioral performance are apparent.

Thus, in trained cats responding to meaningful auditory stimuli, deliberate change in the location of the auditory signal permits some separation of exogenous and endogenous processes in the auditory EP. Short-latency exogenous processes show a dependence of latency and amplitude upon parameters of the physical stimulus, in agreement with the results of other workers who studied responses of untrained animals (*2*). However, the size and shape of longer-latency endogenous processes are relatively independent of the location or intensity of the signal source, and they seem to reflect the significance of the signal (*7*). Further, the evidence suggests that this reflection is dynamic, being most apparent during the decision-making process and relatively less apparent during response execution, once the animal begins to traverse the runway. Since in this paradigm, stimulus significance can be evaluated only by reference to past experience with the experimental cues, we suggest that these endogenous processes reflect the operation of neural mechanisms involved in memory reconstruction.

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3. The runway length was 140 cm from the step-down platform (start) to the center of the L-corner and 170 cm from the center of the L-corner to the step-up food delivery mechanism (goal). The runway was 38 cm wide. Loudspeaker 1 was located at the start end and loudspeaker 2 at the goal end of the L-runway.
4. All click stimuli were delivered from two speakers (Calectro S2-231). Stimuli were produced by delivering a 50-volt pulse for 0.3 msec from a single source, switched to one or the other speaker.
5. Behaviorally, the decision-making period appears to coincide with the orienting response of the cat to the signal. This orienting response to the signal is itself learned and modified during the course of training and overtraining [E. Grastyán and L. Vereczkei, *Behav. Biol.* **10**, 121 (1974)]. At this stage of learning, the orientation of the animals was facing away from speaker 1 and toward the runway. At click onset, the animals would alert (as indicated by a barely discernible head movement), hold that posture for as long as a few seconds, then initiate a slowly accelerating extension toward the alley; the extension would be abruptly transformed into a rapid leap from the platform and crossing of the L-maze. Video analyses indicated that this sequence of behavior was similar whether the CS's were presented at speakers 1 or 2. Although the decision-making period coincides with the motionless phase of the animal's orientation to the signal, the large late component (especially when CS is at the novel 2 position) can remain relatively stable throughout all phases of the animal's behavior (Fig. 1). Therefore, this component is not a consequence of the animal's maintaining a particular posture per se, but, rather, appears to reflect the operation of cognitive processes that normally occur during the motionless orientation phase, but that can continue throughout a variety of postural changes.
6. Compensation was performed by dropping initial time points (sample rate, 1000 per second), essentially shifting the average EP to the left, such that the primary peak appeared at 4 msec for all waves. No compensation was made for the differences in effective stimulus intensity resulting from distance.
7. V. L. Schwent and S. A. Hillyard [*Electroencephalogr. Clin. Neurophysiol.* **38**, 131 (1975)] have observed an early "late" component, 80 to 130 msec to peak (N_1), in the human vertex auditory EP associated with a "finely tuned" selective attention. The most prominent late component associated with stimulus significance in our data on the medial geniculate body of the cat has a substantially shorter latency, 30 to 50 msec to peak, with remarkable consistency in waveshape from animal to animal. Both of these bodies of data indicate that stimulus significance, as opposed to only physical characteristics or position relative to the source, can be reflected in the auditory evoked potential.
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Long-Term Treatment with Lithium Prevents the Development of Dopamine Receptor Supersensitivity

Abstract. *Long-term treatment of rats with haloperidol produced an increased sensitivity to the locomotor and stereotypic effects of apomorphine. This behavioral dopaminergic supersensitivity was accompanied by increased binding of [^{3}H]spiroperidol in the striatum. Rats treated concurrently with lithium and haloperidol failed to develop both behavioral sensitivity to apomorphine and increased striatal dopamine receptor binding. The ability of lithium to prevent recurrent manic-depressive episodes may be related, in part, to its ability to stabilize dopaminergic receptor sensitivity.*

An increased sensitivity to the behavioral effects of drugs that stimulate dopamine receptors is observed after long-term treatment with neuroleptics (*1*), tyrosine hydroxylase inhibitors (*2*), or reserpine (*2, 3*), or after interruption of dopaminergic transmission by lesions of the nigrostriatal dopamine pathway (*4*). Both the supersensitivity induced by chronically administered neuroleptics (*5*) and the nigrostriatal lesions (*6*) are accompanied by an increase in striatal dopamine receptor sites. This apparent proliferation of receptors after blockade of dopaminergic transmission may be causally related to behavioral supersensitivity (*5, 6*).

Changes in catecholamine receptor sensitivity may contribute to a number of human pathological states. Tardive dyskinesia may follow or be intensified by termination of long-term treatment with antipsychotic neuroleptic drugs, and may be related to increased dopamine receptor sensitivity (*7*). Klawans has proposed that lithium may be efficacious in preventing the development of tardive dyskinesia after phenothiazine therapy, since it blocked the increased stereotypy induced by apomorphine after chlorpromazine treatment (*8*). Oscillations in catecholamine receptor sensitivity have also been proposed to be a factor in the etiology of affective disorders (*9*), especially manic-depressive illness (*10*). Since lithium therapy is effective in alle-

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Table 1. Blockade of increased dopamine receptor binding in haloperidol-treated rats by simultaneous treatment with lithium. Rats were injected daily for 21 days with haloperidol (1 mg/kg) or saline. Half of the animals injected with haloperidol and half of the animals injected with saline received a lithium diet. Rats were killed 1 week after the termination of haloperidol and lithium treatment and their corpora striata were rapidly dissected and frozen or assayed immediately for stereospecific [^{3}H]spiroperidol binding. Within each experiment, there was no difference in nonspecific binding (determined in the presence of 1 μM (+)-butaclamol) among all of the treatment groups.

Experiment	Type of tissue	Saline	Haloperidol		Lithium-saline		Lithium-haloperidol	
		Stereospecific binding (count/min)	Stereospecific binding (count/min)	Percent saline control	Stereospecific binding (count/min)	Percent saline control	Stereospcific binding (count/min)	Percent saline control
1	Half fresh, half frozen	2274 ± 171 (20*)	2795 ± 183 (20*)	25†			2583 ± 243 (18*)	13
2	Fresh	1769 ± 84 (9*)	2136 ± 115 (9*)	24‡	1818 ± 72 (10*)	9	1532 ± 181 (8*)	−9§
3	Fresh	1417 ± 82 (10*)	1795 ± 107 (9*)	27†	1472 ± 68 (9*)	4	1283 ± 172 (8*)	−9§
4	Fresh	1317 ± 107 (10*)	1547 ± 120 (10*)	17‡			1349 ± 131 (10*)	2§
5	Half fresh, half frozen	1978 ± 62 (10*)	2392 ± 84 (12*)	21‖	1931 ± 81 (13*)	−2	2197 ± 93 (10*)	11

*Number of determinations of stereospecific [^{3}H]spiroperidol binding, each determination obtained from the triplicate assay of both (+)- and (−)-butaclamol binding on membranes from one rat striatum. †$P < .05$ compared to the saline control. ‡$P < .02$ compared to the saline control. §$P < .05$ between the haloperidol and lithium-haloperidol groups. ‖$P < .001$ compared to the saline control.

viating and preventing the recurrence of manic and manic-depressive symptomatology (*11*), it is of interest to determine whether it alters the development of catecholamine receptor supersensitivity.

We report here that long-term lithium therapy prevents the development of the dopamine receptor supersensitivity that normally accompanies the termination of dopaminergic blockade with haloperidol. This effect of lithium was detectable both as the prevention of increased behavioral sensitivity to apomorphine and the prevention of increased striatal dopamine receptor binding.

Sixty male Sprague-Dawley rats (250 to 300 g) were tested for the effects of lithium on the development of behavioral supersensitivity. A diet of powdered laboratory chow (1500 g) (Purina) mixed with lithium carbonate (2266 mg) in water (2 liters) was fed to 40 animals. We have found that this diet induced lithium levels in rat plasma that were equivalent to therapeutic dosage levels in humans (0.8 to 1.0 meq/liter). The remaining 20 rats were placed on a similar diet without lithium. Half of the rats in each group were injected intraperitoneally with 1 mg of haloperidol per kilogram of body weight daily; the other half in each group received daily injections of saline. Five lithium-treated rats from each subgroup (lithium-haloperidol and lithium-saline) were killed at day 10 and five each were killed at day 21 after drug treatments were started; lithium concentrations in brain and serum were then determined by flame photometry (*12*). On day 22, saline and haloperidol injections were terminated, and all animals were placed on the drug-free diet. After 7 days of no drug treatment, half of the remaining animals in each of the four subgroups were injected with apomorphine (0.5 mg/kg) and placed immediately in covered Plexiglas chambers that were mounted in Motron motility meters (model 40Fc); the other half of the animals were tested the next day. Horizontal and vertical activity was monitored in 15-minute segments for 1 hour. In addition, stereotypy was assessed (*13*) in a 1-minute observation period at the end of each 15-minute monitoring period.

Rats that had been treated only with haloperidol exhibited greater horizontal and vertical activity and stereotypy during the first 30 minutes than animals that had received saline (Fig. 1). Stereotypy and activity scores for animals that had been treated with haloperidol and lithium did not differ from the saline controls.

The absence of supersensitivity to apomorphine in the lithium-haloperidol animals cannot be attributed simply to general depressant effects of lithium that outlasted the termination of treatment, or to residual lithium still present in the animals at the time of testing. The response to apomorphine of animals that had been treated with lithium and injected with saline did not differ from that of animals that had received only saline injections. In addition, lithium levels in the two lithium groups were almost negligible, and were equivalent at the immediate termination of the study (lithium-haloperidol, 0.08 meq per liter of serum, 0.09 meq per kilogram of brain tissue; lithium-saline, 0.00 meq per liter of serum, 0.06 meq per kilogram of brain tissue). Our findings indicate that lithium prevented the development of the dopaminergic behavioral supersensitivity that normally follows continual administration of haloperidol. They further confirm and extend the observations by Klawans on the interactive effects of chlorpromazine and lithium (*8*).

To ascertain whether this lithium effect was related to an inhibition of increased dopamine receptor binding induced by dopaminergic blockade (*5, 6*), 30 rats were divided into three equal groups and given either haloperidol plus lithium, haloperidol, or saline (Table 1, line 1). The same drug dosages and regimens were followed. In four independent replicate experiments (Table 1, lines 2 to 5), lithium treatment was initiated 7 days before the drug injections. In experiments 2, 3, and 5, an additional group (saline plus lithium) was included. Seven days after the termination of drug treatments, the animals were killed and binding assays were performed (*5, 14*). Homogenates (Brinkmann Polytron) of rat corpus striatum in cold tris buffer were washed twice by centrifugation, resuspended in cold 50 mM tris buffer (with 0.1 percent ascorbic acid, 10 μM pargyline, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$; final pH 7.1 at 37°C), warmed to 37°C for 10 minutes, and returned to ice. Each tube received 1 ml of tissue suspension (8 mg of wet tissue) and either 1.5 nM (Table 1, line 1) or 0.5 nM (Table 1, lines 2 to 5) [^{3}H]spiroperidol (26 Ci/mmole) (New England Nuclear). Triplicate tubes were incubated at 37°C for 10 minutes; the reaction mixtures were rapidly filtered at reduced pressure through Whatman GF/B filters with three 5-ml rinses of cold buffer. The radioactivity on the filters was counted by liquid scintillation spectrometry. Specific binding of [^{3}H]spiroperidol, measured as the difference in binding between tubes containing $10^{-6}M$ (+)-butaclamol and tubes containing $10^{-6}M$ (−)-butaclamol, represented about 80 percent of the total binding.

In the in vitro binding experiments (Table 1), haloperidol produced a statistically significant elevation in [^{3}H]spiroperidol binding. Cotreatment with lithium abolished the ability of haloperidol to significantly elevate dopamine receptor binding. Lithium treatment

alone had no significant effect on [^{3}H]spiroperidol binding. In three of the five experiments, there was a statistically significant difference between binding in the haloperidol and haloperidol-lithium groups. In two of the experiments, animals that had been treated with lithium did show a slight increase in [^{3}H]spiroperidol binding after haloperidol treatment, but these increases were not significantly different from controls. The mean increase caused by the haloperidol treatment in all experiments was 23 percent, while when lithium treatment accompanied haloperidol, the mean increase was reduced to 2 percent.

In a separate experiment, striata from each treatment group were pooled and analyzed for binding of between 0.10 to 0.45 n*M* [^{3}H]spiroperidol. A Scatchard plot (data not shown) revealed that the increased binding of the haloperidol-treated group to 32 pmole of binding sites per gram of brain tissue (compared with 20 pmole/g, saline group) was due to an increase in the number of binding sites and not to an alteration in the affinity of the existing binding sites. Striata from rats in the lithium-haloperidol group contained 26 pmole of binding sites per gram of brain tissue, while the rats given lithium alone had 22 pmole/g. The slopes were parallel, again suggesting that alterations in receptor number rather than affinity caused the differences in binding.

Lithium might be expected to prevent the development of haloperidol-induced dopamine receptor sensitivity by increasing the rate of haloperidol excretion, or by decreasing the concentration of haloperidol at dopamine receptors in rat striatum. This seems unlikely since Burt *et al.* (*5*) reported that treatment with 5 mg of haloperidol per kilogram of body weight produced no greater increase in [^{3}H]haloperidol binding than 0.5 mg/kg. Even though the high dose of haloperidol (1 mg/kg) in this study would have been relatively insensitive to small variations in the levels of the drug in the brain, we examined the disposition of [^{3}H]haloperidol in caudates from two groups of 25 rats after treatment with either haloperidol or haloperidol and lithium. Haloperidol or haloperidol and lithium were administered for 21 days, in a manner identical to that for determining [^{3}H]spiroperidol binding. The last dose of haloperidol (1 mg/kg) contained 4.05 μCi of [^{3}H]haloperidol (7.3 Ci/mmole, New England Nuclear). Rats were killed 1, 2, 4, 8, and 24 hours after the final injection, and their striata were removed. No differences in striatal [^{3}H]haloperidol were found between the two groups at any interval tested, ruling out alterations in the disposition of haloperidol as a mechanism of lithium's effect.

We have shown that long-term treatment with lithium prevents the development of dopamine receptor supersensitivity by inhibiting the induction of dopamine receptors caused by haloperidol. Since the processes underlying the induction of membrane receptors are unknown, the mechanism by which lithium prevents an increase in dopamine binding sites is speculative. Although the effects of lithium on cellular processes (*15*) and brain catecholamines (*16*) are complex and varied, these experiments suggest that the ability of lithium to prevent recurrent manic-depressive episodes may be related, at least in part, to its ability to stabilize dopaminergic receptor sensitivity. Whether lithium also interferes with the development of sub- and supersensitivity of other neurotransmitter systems remains to be determined.

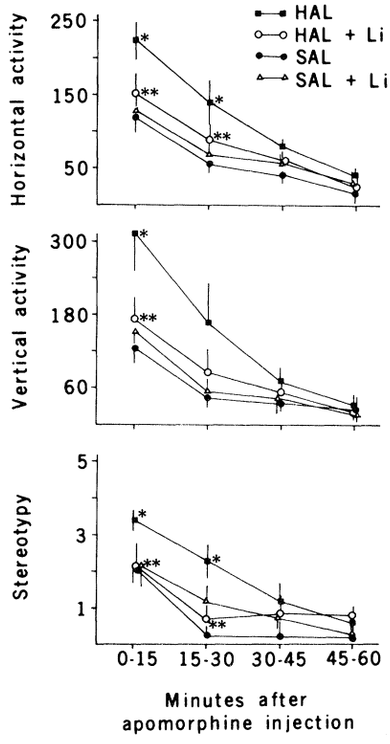

Fig. 1. Effects of lithium on the development of behavioral supersensitivity to apomorphine after haloperidol (1 mg/kg) was injected daily for 3 weeks. Each group contained 10 animals. Half of the animals received a diet supplemented with lithium and half an unsupplemented diet. Half of the animals in each group were injected with haloperidol and half with saline. Seven to eight days after the termination of drug treatment, animals were injected with apomorphine (0.5 mg/kg) and tested for locomotor activity and stereotypy. The decline in the behavioral effects of apomorphine over time is due to the relatively evanescent actions of this compound. Two-way analysis of variance revealed significant ($P < .01$) treatment and time effects on all three measures. *, $P < .05$ for comparisons between haloperidol and saline groups. **, $P < .05$ for comparisons between haloperidol and lithium-haloperidol groups. Abbreviations: *HAL*, haloperidol; *SAL*, saline; *Li*, lithium.

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