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5. Dose-response functions for each animal were obtained by selecting the delay value (from each animal's delay function) at which 75 percent correct performance was obtained. Drug sessions consisted of a 20-trial block at this test delay value and a 20-trial block at 5-second delay, with the order of the blocks counterbalanced across sessions. Data from the 5-second block provided a check on motivation and other general factors affecting performance. Data from the test block were used to construct dose-response functions. Each animal was tested at least twice at each drug dose, and a saline control session was interspersed between each drug test. Dose-response functions were computed for individuals and groups by comparing drug performance to saline performance (mean correct responses after drug divided by mean correct response after saline).
6. Direct infusion of 6-OHDA into neural tissue results in selective damage to catecholaminergic neurons or neuron terminals (or both) (*16*). Noradrenergic neurons exhibit greater selective uptake of the toxin and at appropriate dose levels are selectively destroyed (*17*). Systemic treatment with DMI inhibits noradrenergic membrane reuptake and as a result protects noradrenergic neurons from the cytotoxic effects of 6-OHDA (*18*). The focus of damage is thus shifted to dopaminergic neurons. Substitution of the indoleamine 5,6-DHT for 6-OHDA similarly shifts the focus of damage to serotonergic neurons (*19*).
7. Total quantity of toxin or vehicle varied somewhat between animals, depending upon variation in the length of the principal sulcus. The number of injection sites per hemisphere ranged from 13 to 18 (mean ~ 15). Thus total 6-OHDA dose averaged 3 mg (as free base) and total 5,6-DHT dose averaged 0.27 mg (as free base).
8. Light-microscopic examination of histological preparations revealed that cellular damage in the principal sulcus was confined largely to tracks caused by needle penetrations. Such damage was no greater in the hemisphere injected with 6-OHDA than in the one injected with saline. In both hemispheres, cortex between and adjacent to injection sites in the banks and depths of the principal sulcus and on the dorsal and inferior convexities appeared to be undamaged. Further, the dorsomedial nucleus in the thalamus was intact, except for miniscule islands of chromatolysis and degeneration corresponding to the discontinuous cortical damage at needle penetration sites. The finding that neurons which project to frontal cortex are spared provides evidence that 6-OHDA can be injected intracerebrally without producing widespread nonspecific cortical damage.
9. The degree of protection exerted by DMI on NE terminals was considerably less than expected. The resistance of the monkey to the neurochemical effects of 6-OHDA has been noted [G. R. Breese, R. D. Cooper, A. S. Hollister, G. Kraemer, W. T. McKinney, in *Chemical Tools in Catecholamine Research*, G. Jonsson, T. Malmfors, C. Sachs, Eds. (North-Holland, Amsterdam, 1975), vol. 1, pp. 335-342].
10. The short duration of apomorphine's behavioral action probably contributed to its less reliable therapeutic action. The test procedure took about 20 minutes to complete. Whereas L-dopa was effective for several hours, peak apomorphine effect appeared within 10 to 15 minutes, then rapidly diminished.
11. Clonidine enhanced spatial delayed alternation performance of virtually all animals, both pre- and postoperatively. At optimum dose level (0.01 to 0.04 mg/kg) the mean performance enhancement was as follows: preoperative (N = 4), +11 percent; operated saline controls (N = 4), +23 percent; NE-depleted (N = 2), +18 percent, DA depleted (N = 3), +14 percent; 5-HT depleted (N = 2), +15 percent; and ablated (N = 1), +23 percent.

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Lithium Transport Across Red Cell Membrane: A Cell Membrane Abnormality in Manic-Depressive Illness

Abstract. *In the families of manic-depressive patients, relatives with a history of affective disorders had a significantly higher ratio of mean red cell lithium to plasma lithium in vitro than relatives with no such history. A genetically controlled abnormality in lithium-sodium transport, the mechanism that determines the lithium ratio, may play a role in the etiology of some forms of affective disorders.*

An abnormality in cell membrane function, reflected in altered transport of lithium across cell membranes, may play a role in the etiology of affective disorders (*1*). Using the red cell as a model, we have demonstrated in normal individuals that genetic factors contribute to variability in the distribution of lithium across the red cell membrane, that is, in the ratio of lithium concentration in red cells to that in plasma (lithium ratio) (*2*). An initial study indicated that manic-depressive (bipolar) patients had a significantly higher mean lithium ratio in vivo than normal individuals (*3*). This result suggested that a disturbance in cell membrane function is associated with the pathophysiology of bipolar illness. Before concluding, however, that a genetically controlled biological trait plays a role in the etiology of a psychiatric disorder, one must demonstrate that the biological trait and the psychiatric disorder are transmitted nonindependently within pedigrees (*4*).

We have assessed the lithium ratio in vitro and the psychiatric diagnosis in 66 adult first-degree relatives of 31 bipolar I patients (having both incapacitating manic and depressive states) who were diagnosed according to the Research Diagnostic Criteria (RDC) (*5*). The relatives studied had been drug-free for 1 week and alcohol-free, according to self-report, for 48 hours before participation. Relatives taking medication regularly for a medical or psychiatric illness were excluded from the study.

To determine the lithium ratio, we incubated red cells in the presence of 1.5 mM lithium chloride for 24 hours. The red cell and extracellular lithium concentrations were then determined by atomic emission spectrophotometry. This procedure yields a lithium ratio that is highly correlated (r = .85, P < .001) with the lithium ratio in vivo (*6*). We (E.D., S.E., and R.S.) diagnosed the first-degree relatives according to the RDC by using the *Schedule for Affective Disorders and Schizophrenia—Lifetime Version* (*7*). We did not know the lithium ratios at the time of diagnosis. The laboratory technicians, in turn, did not know the identity or diagnosis of relatives when they conducted the lithium assays.

Of the 66 relatives studied, 16 had a history of a major affective illness, 28 had a history of a minor affective illness, and 22 had no history of affective illness (*8*). The distribution of the lithium ratios of the relatives in each of the three diagnostic groups is shown in Fig. 1. A general linear model two-way analysis of variance (*9*) (the factor entered first was membership in one of the three diagnostic groups and the factor entered second was family membership) indicated significant differences among the mean lithium ratios of the diagnostic groups [F(2, 33) = 3.68, P < .04]. Relatives with a history of major and minor affective illness had significantly higher mean lithium ratios [0.17 ± 0.05 (standard deviation) and 0.18 ± 0.04, respectively] than did relatives with no history of affective illness (0.15 ± 0.03) (t = 2.09, P < .05; and t = 2.45, P < .025, respectively). The differences among means of the groups were not attributable to differences in age, sex, ethnic origin, previous psychotropic medication, or alcoholism (*10*).

Of the 31 bipolar I patients, 15 had on-

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ly one first-degree relative available for study. Of the remaining 16 families, 14 had both affected and unaffected members. Within these 14 families, the affected relatives had a higher mean lithium ratio (0.17 ± 0.03) than the unaffected relatives (0.15 ± 0.02) (paired $t = 1.28$, $P = .07$, one-tailed).

The results of the comparison of affected relatives (those having a history of major or minor affective illness) and unaffected relatives across and within pedigrees indicate that variation in lithium transport across the red cell membrane is associated with the presence or absence of affective illness in relatives of bipolar patients. These results were corroborated by the comparison of relatives of bipolar patients to 291 normal individuals from 120 families. Normal individuals were interviewed briefly to confirm that they and their first-degree relatives were free of primary and secondary affective disorders, schizophrenia, and alcoholism as determined by the criteria of Feighner *et al.* (*11*).

The mean lithium ratio of affected relatives was significantly greater than that of the 291 normal individuals (0.15 ± 0.04, $t = 3.64$, $P < .001$), whereas the mean of unaffected relatives did not differ from that of normal individuals. Each relative was then matched to one normal individual with respect to age, sex, ethnic origin, and socioeconomic status; only one individual from each normal control family was selected. The results were comparable; the mean of the affected relatives was significantly greater than that of normal individuals (0.15 ± 0.03, $t = 4.22$, $P < .001$), whereas the mean of the unaffected relatives did not differ from that of normal individuals.

What is the significance of an association between lithium transport and affective illness in families of bipolar patients? (i) Affective illness may have a secondary effect on cell membrane function. Since all but five of the affected relatives were free of psychiatric illness at the time of the study and had not recently had an affective illness, such a secondary effect would appear to be irreversible. This interpretation, therefore, seems unlikely. (ii) Genetically controlled cell membrane properties may play a role in vulnerability to affective disorders. According to this interpretation, individuals with cell membrane abnormalities that lead to high intracellular concentrations of lithium would be at greater risk for affective disorders than other individuals. This interpretation can best be confirmed by prospective studies.

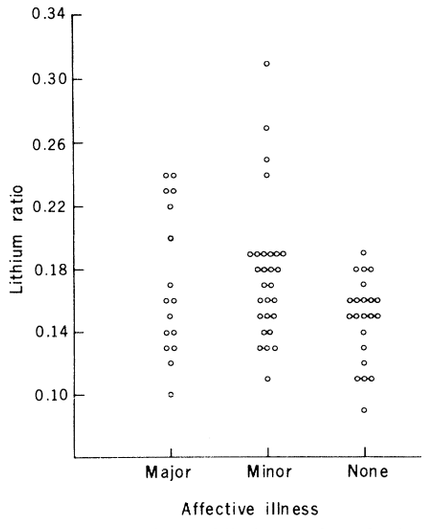

Fig. 1. Distributions of lithium ratios of relatives having history of major affective illness, minor affective illness, or no affective illness.

Several operationally distinct mechanisms of lithium transport across the red cell membrane have been elucidated (*12*). The primary mechanism controlling the distribution of lithium is a lithium-sodium counterflow system that transports lithium against its electrochemical potential gradient. Transport of lithium is driven by an oppositely directed sodium electrochemical potential gradient. The lithium-sodium counterflow system is mediated by a lithium-sodium exchange mechanism. In the absence of lithium under physiological conditions, this exchange mechanism is primarily involved in sodium-sodium exchange. The lithium ratio in vivo has a significant inverse correlation with lithium-sodium counterflow (*13*). The lithium ratio in vitro assessed in this study, which began before the description of lithium transport mechanisms, is therefore an indirect measure of counterflow. Initial evidence indicates that lithium-sodium counterflow is under genetic control (*13, 14*).

When lithium transport measures are compared in patients with affective disorders and in normal individuals, the results are equivocal (*13, 15*). One possible explanation for these conflicting results is that patients with affective disorders may be genetically heterogeneous with respect to cell membrane functioning. For example, a higher mean lithium ratio in vivo was found in bipolar patients whose first-degree relatives had affective illness than in bipolar patients whose first-degree relatives had no such illness (*16*). The pedigree study presented here, together with advances in our understanding of lithium transport in red cells, suggest that if a cell membrane abnormality is involved in the transmission of some forms of bipolar illness, the abnormality may be in the lithium-sodium (sodium-sodium) exchange system.

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8. Relatives of bipolar I patients were considered to have a history of major affective illness if they were given one of the following RDC diagnoses: major depressive disorder, manic disorder, bipolar I or II, or schizoaffective disorder. Relatives were considered to have a history of minor affective illness if they had no major affective illness and were given one of the following diagnoses: minor depressive disorder, intermittent depressive disorder, or hypomanic disorder. Relatives were considered to have no history of affective illness if they had a personality disorder, other diagnoses such as generalized anxiety disorder, or no psychiatric condition. Relatives with only a diagnosis of alcoholism were considered to have a major affective illness. No relative was given a diagnosis of schizophrenia.
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lithium ratio, the two-way analysis of variance was repeated excluding the five relatives with a diagnosis of alcoholism. Significant differences among the mean lithium ratios of the three diagnostic groups remained [$F(2, 29) = 3.89$, $P < .04$)]. The significant differences among groups therefore cannot be attributed to elevations in the lithium ratio in affected relatives with alcoholism.
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Bitter Taste of Saccharin Related to the Genetic Ability to Taste the Bitter Substance 6-*n*-Propylthiouracil

Abstract. *Bitter taste thresholds for* 6-n-*propylthiouracil are bimodally distributed, dividing subjects into tasters and nontasters. Their taste worlds differ with regard to the sweetness of sucrose and saccharin and to the bitterness of saccharin. These differences suggest that nontasters tend to perceive less bitterness in saccharin at concentrations used in beverages.*

Saccharin tastes bitter as well as sweet to many individuals. The data reported here suggest that the intensity of the bitter taste of saccharin is related to the genetically determined ability to taste 6-*n*-propylthiouracil (PROP).

Taste thresholds for the bitter substances PROP, phenylthiocarbamide or phenylthiourea (PTC), and other compounds containing the -N-C=S group show a bimodal distribution (*1*). Family studies have generally concluded that those least sensitive to PROP (nontasters) carry two recessive genes for taste blindness to PROP; the most sensitive (tasters) are either heterozygous or homozygous for the dominant gene (*2*).

In the present study 20 tasters and 20 nontasters of PROP (*3, 4*) scaled the intensities of the sweet, salty, sour, and bitter taste qualities of sodium saccharin, sodium chloride (NaCl), quinine hydrochloride (QHCl), and sucrose (*5*) according to Stevens's (*6*) method of magnitude estimation as modified by Smith and McBurney (*7*). Figure 1 shows the bitterness and sweetness of sodium saccharin. As a means of averaging the magnitude estimates of different subjects, each subject's estimates are expressed relative to that subject's estimate of the intensity of 0.32*M* NaCl (*8*). Saccharin tastes significantly less bitter (relative to 0.32*M* NaCl) to nontasters than to tasters at the two lowest concentrations (*9*). The concentration of sodium saccharin used in many diet beverages is about 0.0010 to 0.0015*M* (*10*). Note that at these concentrations the average bitterness attributed to sodium saccharin by PROP nontasters is one-third to one-half that of PROP tasters.

The distribution of bitter responses in the two groups is of special interest. There is considerable overlap, so that some tasters produce low estimates of the magnitude of the bitterness of saccharin that are similar to those of nontasters. However, one group of tasters gave estimates of the bitterness of the weakest saccharin that were higher than those of any nontaster. One nontaster reported essentially no bitterness at any concentration of saccharin tested. This overlap is much greater than that seen in the bimodal distribution for PROP itself.

Previous work indicated that tasters and nontasters did not differ with regard to sensitivity to saccharin (*11*). However, the thresholds measured were for the sweetness of saccharin, not its bitterness. In general, a molecule could contain the -N-C=S group but fail to show a bimodal threshold distribution if some other features of the molecular configuration produced taste sensations at lower concentrations. In such a case, scaling the perceived intensity of suprathreshold concentrations could reveal differences between tasters and nontasters because the -N-C=S group would add to the perceived intensity at concentrations above its threshold.

Saccharin does not contain the -N-C=S group originally believed to be necessary for the bimodal bitter threshold distribution. Two other compounds without this group, anethole trithione and caffeine, also have bitter tastes related to that of PROP (*12, 13*). Fischer (*4*) and Beets (*14*) suggested that the original -N-C=S structure may be too restrictive. For example, Fischer (*4*) proposed

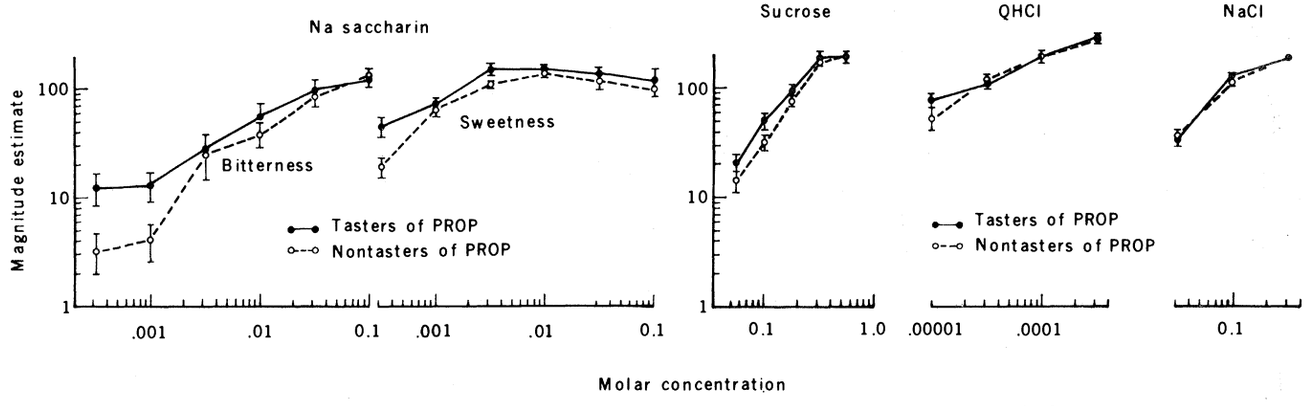

Fig. 1 (left). Magnitude estimates ±1 standard error (S.E.) of the sweetness and bitterness of sodium saccharin for tasters and nontasters of PROP. Fig. 2 (right). Magnitude estimates ±1 S.E. of the sweetness of sucrose, bitterness of QHCl, and saltiness of NaCl for tasters and nontasters of PROP.

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