that DNA from AGM cells also speeded up the reassociation of ^{3}H-labeled Ki-MuLV DNA, although the effect was much less than that of any of the rodent DNA's tested. The number of viral equivalents per diploid cell can be calculated from these data and is listed in Table 1.

Our results indicate that at least two classes of double-stranded DNA are synthesized by the RNA-dependent DNA polymerase of Ki-MuLV. The major class of DNA represents the selective transcription of a relatively small portion of the viral RNA. It is not clear whether the dominant double-stranded DNA product is an artifact of the in vitro reaction or whether it represents a functionally important gene product. It has been shown that 70*S* viral RNA can be dissociated by heat or treatment with dimethyl sulfoxide into several major subunits each with a molecular weight of about 3×10^6 (*14*). Such a subunit or portion of it may function as a template and generate double-stranded DNA having the reassociation characteristics shown in Fig. 1. Although it was a minor fraction, there was a class of double-stranded DNA that approximated the size of the entire viral genome.

It is possible that the in vitro viral DNA also plays a role in viral replication in vivo and may represent a form of the viral genome that can be integrated into host DNA during the process of transformation. However, it is not yet clear whether these in vitro DNA products are related in any way to the replicative or oncogenic potential of RNA tumor viruses. The process of transformation with RNA tumor viruses may be similar to that reported with oncogenic DNA viruses; the latter are thought to be integrated into the genome of transformed cells (*15*). With the DNA tumor virus SV40, normal uninfected cells appear to contain only a partial copy of the DNA viral genome (*11*). When labeled Ki-MuLV double-stranded DNA with an informational content equivalent to that of a molecule having a molecular weight of 5×10^6 was used as a probe to detect "integrated" viral DNA sequences, normal and transformed cell DNA's could not be differentiated (Fig. 3). In addition, the number of "integrated" genome equivalents detected in these cells exceeded that for comparable DNA tumor viruses by as much as 50-fold (*11*). Our results imply the presence of mammalian polynucleotide sequences within the viral RNA genome. Perhaps a more valid probe would be the in vitro DNA product with the informational content of the entire viral genome. The relation between the polynucleotide sequences shared by the major double-stranded DNA product and the normal cell genome is not yet known.

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Rubidium and Lithium: Opposite Effects on Amine-Mediated Excitement

Abstract. *In mice the activation caused by morphine was antagonized by previous treatment with lithium and was potentiated by previous treatment with rubidium. Other antimanic drugs antagonized the morphine activation as well. The effect of rubidium was similar to that of the antidepressant drugs imipramine and pargyline. Rubidium may merit clinical evaluation as an antidepressant agent in man.*

The alkali metal lithium is a useful agent for the treatment of acute mania (*1*) and may also be of value in the prevention of recurrent manic and depressive illnesses (*2*). The lithium ion is thought to act through an effect on monoamine metabolism in the brain (*3*); the neuropharmacology of lithium indirectly supports the monoamine theory of depression (*4*). Rubidium is an alkaline earth metal of the same series as lithium, but it possesses contrasting properties. Its effects on the binding of sodium and potassium to a preparation of neuronal membrane ganglioside in vitro (*5*) are opposite to those of lithium (*6*). Rubidium causes increased activity, aggression, and electroencephalogram (EEG) activation in monkeys; whereas lithium produces EEG slowing and reduces hyperactivity (*6*). Recently these two ions were shown to have opposite effects on brain norepinephrine (NE) metabolism in rats (*7*). Rubidium produces a marked shift in the metabolism of NE toward normetanephrine formation; this action of rubidium is similar to the effect of imipramine on NE metabolism (*8*). Lithium, on the other hand, alters NE catabolism toward deamination and decreases normetanephrine formation (*9*). Both ions cause an increase in the rate of disappearance of NE from brain; the increased turnover seen with lithium may reflect intraneuronal NE degradation, whereas the pattern of catabolite production after treatment with rubidium indicates increased release of physiologically active NE (*7*). Rats treated with rubidium became aggressive and irritable when handled. These effects on behavior and NE metabolism have suggested a possible use for rubidium in the treatment of depression (*6*, *7*). However, the behavioral actions of rubidium have not previously been compared directly with those of known antidepressant drugs.

Our experiments were designed to evaluate the effects of the two ions on

Table 1. Activity of groups of control and previously treated mice after being given morphine. Counts are expressed as the mean percentage (and standard deviation) of the activity of the control groups at 60 minutes. Three 1-minute counts were made of each group at −30, 0, 30, 60, 90, and 120 minutes.

Treatment	Groups (No.)	Number of 1-minute activity counts	Activity (%)					
			−30	0	30	60	90	120
Saline	10	30	3.4 ± 5.1	11.3 ± 5.7	73.5 ± 24.7	100 ± 30.4	77.8 ± 31.9	32.2 ± 15.2
Lithium	10	30	3.4 ± 5.7	6.0 ± 4.1*	56.8 ± 19.0†	60.3 ± 21.8*	58.7 ± 24.7‡	36.0 ± 11.4
Saline	6	18	4.9 ± 4.9	10.0 ± 8.3	85 ± 22	100 ± 15.2	53 ± 14.7	18 ± 9.8
Rubidium	6	18	6.6 ± 5.6	13.1 ± 4.9	162 ± 41.6*	155 ± 30.1*	73 ± 19.1†	30 ± 12.7†

* Differs from control at $P < .001$. † Differs at $P < .01$. ‡ Differs at $P < .02$.

a behavioral state which is mediated by central monoamines. The activation produced in mice by morphine (*10*) was used for this purpose. After repeated injections of morphine the turnover rates of NE and 5-hydroxytryptamine (5-HT) are increased in animal brains (*11*, *12*). A single dose produces a marked decrease in amounts of NE and 5-HT in brain (*13*) and increases the rate of disappearance of dopamine from central neurons (*14*). Behavioral responses to morphine in rats are modified after inhibition of synthesis of catechol and indole amines (*15*). Our own data clearly implicate both types of monoamines in the murine activation response.

Male albino Swiss mice (20 to 24 g, CSL strain), housed in groups of six, received a single intraperitoneal injection of morphine sulfate (25 mg/kg). The motor activation produced was measured over 2 hours. Lithium ion (as LiCl) was given to ten groups in a dose of 5 meq kg^{-1} day^{-1} for 4 days as well as 30 minutes before injection of morphine. These animals had plasma lithium levels of 0.4 meq/liter 150 minutes after the last dose. No sedation was produced by this dosage schedule. Rubidium ion (as RbCl) was given to six groups in a dose of 3 meq kg^{-1} day^{-1} for 2 days and 30 minutes before injection of morphine. No alteration of gross behavior was observed in these mice. Control groups received sodium chloride (5 meq/kg or 3 meq/kg, respectively) at the same times as the experimental groups. In each experiment the response to morphine of one group treated with lithium or rubidium was compared with that of the appropriate control group. Naive mice were used in all experiments.

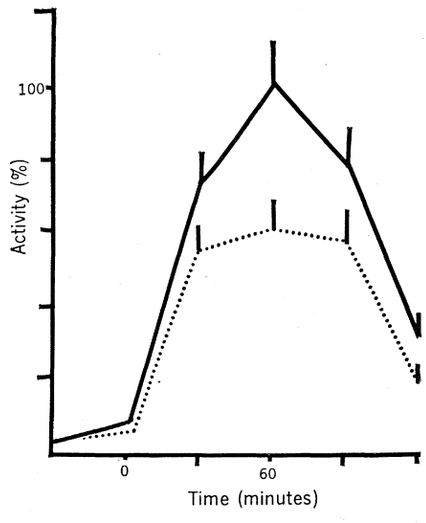

Fig. 1. Activity of ten groups of mice treated with lithium and ten control groups treated with saline. Morphine sulfate (25 mg/kg) was injected intraperitoneally at 0 minute. Activity was expressed as the percentage of activity of control groups at 60 minutes. Vertical bars indicate standard errors of means. Solid line, saline; dotted line, lithium.

The control mice exhibited intense stereotyped hyperactivity which commenced 15 to 20 minutes after injection of morphine, reached a peak at 60 minutes, and declined in about 120 minutes. Treatment with lithium significantly reduced this activation. In contrast, groups treated with rubidium showed a markedly increased response to morphine (Table 1 and Figs. 1 and 2).

Our findings complement the earlier observations that lithium and rubidium ions have opposite effects on behavior (*6*, *7*). We have found that other psychoactive drugs modify the activation by morphine in characteristic ways. All drugs effective in treating mania, as well as lithium, antagonize the excitement; the drugs studied in this category include haloperidol, chlorpromazine, cinanserin (*16*), and methysergide (*17*). Antidepressant drugs of both the tricyclic (imipramine) and monoamine oxidase inhibitor type (pargyline) potentiate the activation caused by morphine. The effect of rubidium is thus similar to that of known antidepressants. The monoamine precursors dihydroxyphenylalanine and 5-hydroxytryptophan also potentiate the response of mice to single injections of morphine; both these amino acids have been reported to have antidepressant activity in some patients (*18*, *19*). Finally, we have found that depletion of either catechol or indole amines by α-methylparatyrosine or parachlorophenylalanine reduces the behavioral response to morphine. The former drug has been successfully used to treat clinical mania (*20*).

The contrasting effects of antidepressants and antimanic agents on the excitement syndrome caused by morphine in mice have led us to pro-

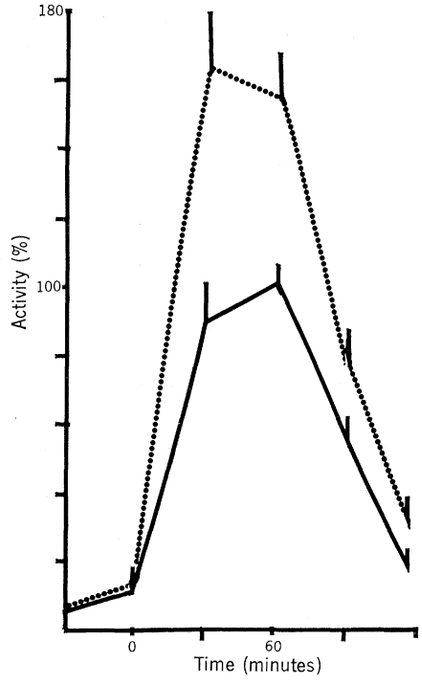

Fig. 2. Activity of six groups of mice treated with rubidium and six control groups treated with saline. Morphine sulfate (25 mg/kg) was injected intraperitoneally at 0 minute. Activity was expressed as the percentage of activity of control groups at 60 minutes. Vertical bars indicate standard errors of means. Solid line, saline; dotted line, rubidium.

pose this activated state as an animal model of mania (*21*). Rubidium clearly potentiated the model excitement, and this effect was consistent with that of known antidepressants; lithium had the opposite effect. These results suggest that rubidium merits clinical evaluation as an antidepressant agent in man.

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Evoked Potential Correlates of Auditory Signal Detection

Abstract. *A long-latency component of the averaged evoked potential recorded from the human scalp varied in close relationship with subjects' perceptual reports in an auditory signal detection task. Detected signals evoked potentials several times larger than did undetected signals, falsely reported signals, or correctly reported nonsignals. The threshold signal intensity at which detection performance exceeded chance levels was identical with concurrently obtained electrophysiological measures of threshold.*

The properties of averaged evoked potentials (AEP's) recorded from the human scalp represent important information about the cerebral processes that underlie perception. Reliable changes in certain components of the AEP are associated with numerous types of perceptual and psychophysical judgments (*1*) and with the detection, discrimination, and interpretation of sensory input (*2–5*). One vital test of the validity of the AEP as a measure of perceptual processes in man is its relationship to the detection of stimuli near the threshold of sensation. Although many investigators have reported that AEP indices of signal detectability are nearly as sensitive as the observer's perceptual reports (*6*), two recent studies reported wide discrepancies between psychophysical and AEP measures of absolute sensory threshold (*7, 8*). As a result one group was led to conclude that "evoked activity . . . may play no essential or important role in determining perceptual reactions" (*8*).

Such conclusions were challenged by Donchin and Sutton (*9*), who enumerated serious methodological problems with the design and interpretation of AEP studies of threshold in general. First, in order to obtain a meaningful correlation between electrophysiological and perceptual responses, they must be obtained concurrently during the actual psychophysical task, since the AEP is highly sensitive to changes in the behavioral or attentive state of the observer (*10*). This is particularly true in the case of the long-latency, positive "P300" component of the AEP (*11*), which is reportedly enhanced during the detection of faint signals in any modality (*3, 5, 12, 13*). Second, prior studies of threshold were criticized (*9*) for failing to take into account the effect of observers' response biases and the type of psychophysical procedures used for threshold determinations. Psychophysical reports of threshold signals are codetermined by two factors: the observer's decision criterion of how intense a sensation must be in order to be reported as a signal, and the sensitivity of his perceptual system in distinguishing signals from background noise. If variations in the criterion factor are uncontrolled, artificial dissociations between perceptual and AEP measures of threshold may result (*14*). In the study reported here, we demonstrate that, when these critical methodological necessities are observed, the P300 component of the AEP does in fact bear close correspondence to behavioral measures of the perception of near-threshold stimuli.

We used a signal detection procedure in which the observer's task was to decide on each trial whether or not an acoustic signal at threshold level (presented on a probabilistic basis) had been added to the continuous background noise. The AEP's were computer-averaged separately for each of the four possible combinations of signal conditions and observer's responses: detected signals (hits), failures to detect signals (misses), incorrect reports of signal presence (false alarms), and correct reports of signal absence (correct rejections). Separate computer averaging permitted an assessment of whether perceptually distinctive events were associated with different AEP wave forms. Furthermore, this method enabled us to evaluate directly the relation between the AEP and a measure of perceptual sensitivity (d') that is independent of possible variations in criterion and is closely tied to the extrac-

Table 1. Area measure of P300 magnitude (microvolts × milliseconds) on different types of trials in auditory detection task when cue light was present in the signal interval. Each tabular value is averaged over eight to ten blocks of trials and across the three observers. The probability values given in the footnotes indicate the statistical significance of difference in P300 magnitude from hit trials (two-tailed *t*-tests); F.A., false alarms; C.R., correct rejections.

Type of trial	Performance level: correct detections (%)		
	50–69	70–89	90 +
Hit	470	639	703
Miss	269*	427*	
F.A.	250*	313†	
C.R.	281*	308†	300†

* $P < .005$. † $P < .001$.