contractile responses to vasoactive agents in the absence of Mg^{2+} are probably also due to enhanced influx or translocation of Ca^{2+} into the vascular muscle cells. It is known that all of these vasoactive agents utilize calcium (that is, extracellular, membrane-bound, or intracellular) for eliciting contractile responses (*18*). This is consistent with the finding of a decreased ratio of magnesium to calcium in the heart muscle of SDIHD groups (*2-4*).

It is very unlikely that changes in receptor affinities could cause the increased or decreased contractile tensions in response to extracellular Mg^{2+}, since similar changes in tension in response to a nonspecific vasoactive agent, KCl, were also obtained. Potassium-induced responses were shown in our studies to be mediated directly rather than indirectly through the release of any known neurotransmitter substance, since a variety of specific antagonists did not modify the response (*19*).

The influence of Mg^{2+} could also, possibly, be explained in terms of an effect on adenosine 3′,5′-monophosphate (cyclic AMP) formation within the cells; Mg^{2+} being an activator of adenylate cyclase (*20*), an enzyme involved in the synthesis of cyclic AMP. There is experimental evidence to suggest that increased and decreased cyclic AMP concentrations participate in coronary vasodilatation and constriction, respectively (*21*). A decrease in cyclic AMP in the absence of Mg^{2+} could result in an increased concentration of free calcium ions within the cytoplasm because there would be less cyclic AMP–mediated calcium sequestration. Thus, this mechanism could, in part, be responsible for the increased tone and reactivity of coronary arteries obtained in the absence of Mg^{2+}. An alternative and contributing mechanism could be an inhibition of a Ca^{2+}-dependent adenosinetriphosphatase at the membrane that is Mg^{2+}-dependent and that presumably extrudes Ca^{2+} (*22*).

Thus our results, which demonstrate that reduced magnesium in the coronary vasculature environment exerts profound influences on coronary vascular tone and reactivity, support the hypothesis that hypomagnesemia could produce progressive vasoconstriction, resulting in coronary arterial spasm and, finally, SDIHD (*11*).

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References and Notes

1. T. Crawford and M. D. Crawford, *Lancet* **1967-I**, 229 (1967).
2. B. Chipperfield and J. R. Chipperfield, *ibid.* **1973-II**, 293 (1973); M. S. Seelig and H. A. Heggetveit, *Am. J. Clin. Nutr.* **27**, 59 (1974); T. W. Anderson, D. Hewitt, L. C. Neri, G. Schreiber, F. Talbot, *Lancet* **1973-II**, 1390 (1973); J. R. Marier, *Rev. Can. Biol.* **37**, 115 (1978); *Natl. Res. Counc. Can. Publ.* No. 17581 (Ottawa, 1979).
3. B. Chipperfield and J. R. Chipperfield, *Am. Heart J.* **95**, 932 (1978).
4. H. Karppanen, R. Pennanen, L. Passinen, *Adv. Cardiol.* **25**, 9 (1978).
5. G. Behr and P. Burton, *Lancet* **1973-II**, 450 (1973); C. J. Johnson, D. R. Peterson, E. K. Smith, *Am. J. Clin. Nutr.* **32**, 967 (1979).
6. B. T. Altura and B. M. Altura, in *Microcirculation*, G. Kaley and B. M. Altura, Eds. (University Park Press, Baltimore, 1978), vol. 2, p. 590; F. J. Haddy and M. S. Seelig, in *Magnesium in Health and Disease*, M. Cantin and M. S. Seelig, Eds. (Spectrum, Jamaica, N.Y., in press).
7. B. M. Altura and B. T. Altura, in *Prostaglandins in Cardiovascular Function*, S. Greenberg, T. Burks, P. J. Kadowitz, Eds. (Dekker, New York, in press).
8. ———, *Microvasc. Res.* **7**, 145 (1974).
9. ———, *Proc. Soc. Exp. Biol. Med.* **151**, 752 (1976); *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **35**, 2360 (1976); in *Excitation-Contraction Coupling in Smooth Muscle*, R. Casteels, T. Godfraind, J. C. Ruegg, Eds. (Elsevier/North-Holland, Amsterdam, 1977), p. 137; S. B. Sigurdsson and B. Uvelius, *Acta Physiol. Scand.* **99**, 368 (1977); B. M. Altura, *Artery* **4**, 512 (1978).
10. B. M. Altura and B. T. Altura, *Blood Vessels* **15**, 5 (1978).
11. B. M. Altura, *Med. Hypoth.* **5**, 843 (1979).
12. ———, *Am. Heart J.* **72**, 709 (1966).
13. ——— and B. T. Altura, *Am. J. Physiol.* **220**, 938 (1971).
14. ———, *Artery* **3**, 72 (1977); M. Fujiwara, H. Kitagawa, K. Kurahashi, *Br. J. Pharmacol.* **63**, 51 (1978).
15. B. T. Altura and B. M. Altura, in *Magnesium in Health and Disease*, M. Cantin and M. S. Seelig, Eds. (Spectrum, Jamaica, N.Y., in press); S. Goldstein and T. T. Zsoter, *Br. J. Pharmacol.* **62**, 507 (1978).
16. P. D. M. V. Turlapaty and O. Carrier, Jr., *J. Pharmacol. Exp. Ther.* **187**, 86 (1973); H. A. Jurevics and O. Carrier, Jr., *Am. J. Physiol.* **225**, 1479 (1973); P. D. M. V. Turlapaty, O. Carrier, Jr., H. Jurevics, *J. Pharmacol. Exp. Ther.* **192**, 372 (1975); O. Carrier, Jr., R. K. Hester, M. A. Jurevics, T. E. Tenner, *Blood Vessels* **13**, 321 (1976).
17. P. D. M. V. Turlapaty and B. M. Altura, *Eur. J. Pharmacol.* **52**, 421 (1978).
18. G. B. Weiss, *Adv. Gen. Cell Pharmacol.* **2**, 71 (1977).
19. P. D. M. V. Turlapaty and B. M. Altura, unpublished observations.
20. D. L. Garbers and R. A. Johnson, *J. Biol. Chem.* **250**, 8449 (1975); C. Londos and M. S. Preston, *ibid.* **252**, 5957 (1977); S. J. Bird and M. E. Maguire, *ibid.* **253**, 8826 (1978).
21. T. W. Anderson, L. C. Neri, G. B. Schreiber, F. D. F. Talbot, A. Zdrorewski, *Can. Med. Assoc. J.* **113**, 199 (1975).
22. L. M. Popescu, in *Excitation-Contraction Coupling in Smooth Muscle*, R. Casteels, T. Godfraind, J. C. Ruegg, Eds. (Elsevier/North-Holland, Amsterdam, 1977), p. 13.
23. Supported in part by PHS research grants NHLBI-18015 and DA-02339. We thank M. Vassalle for supplying some of the animals used in these studies, B. T. Altura for reviewing the manuscript and for helpful suggestions. Correspondence should be addressed to B.M.A.

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Faster Cholinergic REM Sleep Induction in Euthymic Patients with Primary Affective Illness

Abstract. *Arecoline, a cholinergic muscarinic receptor agonist, induced rapid eye movement sleep significantly more rapidly in patients with primary affective illness in remission than in normal control subjects matched for age and sex. These results, and others, suggest that patients with primary affective illness may have a supersensitive cholinergic system both when they are ill and when their symptoms are in clinical remission.*

Sleep disturbance is one of the most characteristic biological findings in patients with primary affective illness. The sleep of depressed patients is normally short, shallow, and fragmented; REM latency [the time from sleep onset to the first rapid eye movement (REM) period] is short (*1*). Since cholinergic mechanisms are involved in both arousal and the induction of REM sleep (*2*), we previously suggested that activation of central cholinergic neurons or supersensitive cholinergic receptors may be implicated in the pathophysiology of sleep disturbance in depression (*3*). This interpretation is consistent with the hypothesis that an increased ratio of cholinergic to noradrenergic activity underlies depression (*4*).

To test the hypothesis further, we compared patients with primary affective illness whose symptoms were in remission with normal control subjects on the cholinergic REM-induction test. In this test we measure the speed with which REM sleep is induced by arecoline, a cholinergic muscarinic agonist administered intravenously during non-REM sleep. We had previously used this technique to provide evidence that muscarinic supersensitivity develops in normal volunteers who receive scopolamine, a cholinergic muscarinic receptor blocker, in the morning for two or more consecutive days (*5*).

The control subjects were 16 paid normal volunteers [nine males, seven females, mean age ± standard deviation (S.D.) = 28.3 ± 5.4 years]. They were compared with two groups of patients with primary affective illness whose symptoms were in remission. The initial group (group 1) of 13 patients (four males, nine females, 12 bipolar and 1 unipolar, mean age = 28.9 ± 6.9 years) were tested after all their regular medica-

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tions had been discontinued for at least 2 weeks. They had previously received lithium carbonate (900 to 2100 mg/day); some had also received other psychotherapeutic medications, including tricycylic antidepressants (N = 3), tranylcypromine (N = 1), thioridazine (N = 1), and chlorpromazine (N = 1). To rule out potential confounding effects of prior psychoactive drug treatment or withdrawal on the arecoline response of group 1, we recruited a second group of eight patients who had never received any somatic therapy (N = 4) or had not received it within 4 months of the study (N = 4). Group 2 consisted of six bipolar and two unipolar affective patients (three males, five females, age = 29.1 ± 5.6 years). All patients met research diagnostic criteria for primary affective illness (*6*) and had been in clinical remission for at least 3 months at the time of the study (*7*).

Techniques of polygraphic sleep recordings and administration of intravenous drug or placebo infusions during sleep have been described (*2, 8*). After one or two adaptation nights in the sleep laboratory (*9*), the subject slept with an intravenous catheter attached to polyethylene tubing extending out of the room. A peripheral anticholinergic agent, methscopolamine (0.3 mg), was administered intravenously at the end of the first REM period to prevent peripheral cholinergic side effects of arecoline. By itself, methscopolamine does not affect the human sleep electroencephalogram (*10*). Each subject then received one intravenous infusion each night administered over a 3-minute period and timed to end 25 minutes after completion of the first REM period (*11*). During the initial study of normal subjects and group 1 patients, the following infusions were administered in random order and on nonconsecutive nights: (i) placebo (isotonic saline); (ii) arecoline, 0.5 mg; and (iii) arecoline, 1.0 mg. In the second study, of group 2 patients and normal subjects, only placebo and 0.5-mg doses of arecoline were given in random order.

The absence of a difference in the mean latency from infusion to the second REM period (inf-REM_2 latency) after placebo infusion between normal subjects and patients (Table 1) confirmed our expectation based on prior studies (*11*) that the second non-REM period would be of normal duration in affective illness. Likewise, REM latency did not significantly differ among the three groups (normal subjects, 76 ± 28 minutes; group 1, 64 ± 25 minutes; and group 2, 61 ± 20 minutes), indicating that the shortened REM latency seen during the depressed state returns toward normal during remission.

Table 1. Time (in minutes) from infusion to the onset of the second REM period.

Treatment	Normal subjects		Patients			
			Group 1		Group 2	
	N	Mean ± S.D.	N	Mean ± S.D.	N	Mean ± S.D.
Placebo	16	53.6 ± 14.1	11	49.5 ± 18.2	8	48.2 ± 13.0
Arecoline						
0.5 mg*	12	37.5 ± 21.9	9†	11.0 ± 6.3‡	8	14.1 ± 7.9§
1.0 mg	10†	19.3 ± 12.0	9†	7.1 ± 3.9‡		

*Kruskal-Wallis one-way analysis of variance, H = 10.22, $P < .01$. †Data from subjects who wakened for longer than 3 minutes within 15 minutes of an infusion were disregarded (*2*). ‡$P < .01$. §$P < .025$. Statistical comparisons between normal subjects and patient groups were made with Mann-Whitney U tests.

The inf-REM_2 latency was significantly shorter after arecoline than after placebo in both normal subjects and patients. The effect was dose dependent (Table 1). This finding is consistent with our previous data indicating that arecoline and physostigmine induce REM sleep (*2*). Arecoline also induced REM sleep significantly sooner in both patient groups than in controls (Table 1).

Since the patients in group 2 had either never been treated with psychotropic medication or had been completely drug-free for at least 4 months, it is unlikely that the supersensitive REM induction response to arecoline resulted from prior drug administration or drug withdrawal. The cholinergic REM induction response per se was not significantly correlated in any subject group with age, sex, weight, or sleep EEG measures such as REM latency, duration and number of eye movements during the first REM period, time spent in various sleep stages before the infusion, or the real (chronological) time of infusion. In addition, there was no significant difference between subject groups in any of the above variables. Preliminary evidence from another ongoing study of hospitalized patients in a depressed state also indicates a faster REM induction response to arecoline (*12*).

The physiological mechanisms underlying our finding are not fully understood. Our understanding is limited by the absence of detailed anatomical information about cholinergic pathways within the brain (*13*). In addition, although cholinergic neurons undoubtedly affect and are affected by neurons using norepinephrine, serotonin, dopamine, and other neurotransmitters, the precise relationships and sites of interaction in the regulation of sleep and affect remain speculative (*14*). While arecoline may have produced the results by interacting with supersensitive cholinergic receptors, further data are required to support that hypothesis. The receptors' locations and whether they are presynaptic or postsynaptic, excitatory or inhibitory, are also unknown. The cholinergic REM induction effect may also be mediated through another system, such as an abnormality in aminergic neurons. It is unlikely that cholinergic mechanisms per se explain either the sleep disturbance or the mood alterations in the depressive syndromes. (i) Even though our patients showed faster cholinergic REM induction, they did not display some of the other stigmata of the sleep disturbance of actively ill patients with primary depression, such as short REM latency on baseline or placebo nights. (ii) Others have reported that administration of cholinomimetic agents, such as physostigmine or choline (the biosynthetic precursor of acetylcholine), may induce depression in patients with a history of affective illness but produce little or no mood change in normal volunteers (*15*).

These findings suggest that a hyperresponsive cholinergic mechanism is continuously present, whether the patient is ill or well, and that it may underlie primary affective illness, possibly as a predisposing factor. It remains to be seen whether the cholinergic REM induction test could be used in future genetic studies to identify subjects at risk for affective illness.

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References and Notes

1. D. J. Kupfer, *Biol. Psychiatry* **11**, 159 (1976); G. Vogel, F. Vogel, R. S. McAbee, J. A. Thurmond, *Arch. Gen. Psychiatry*, in press; J. C. Gillin, W. C. Duncan, K. D. Pettigrew, B. L. Frankel, F. Snyder, *ibid.* **36**, 35 (1979).
2. N. Sitaram, R. J. Wyatt, S. Dawson, J. C. Gillin, *Science* **191**, 1281 (1976); J. C. Gillin, N. Sitaram, W. B. Mendelson, R. J. Wyatt, *Psychopharmacologia* **58**, 111 (1978); N. Sitaram, A. M. Moore, J. C. Gillin, *Nature (London)* **274**, 490 (1978).
3. J. C. Gillin, N. Sitaram, W. C. Duncan, *Psychiatr. Res.* **1**, 17 (1979).
4. D. C. Janowsky, M. K. El-Yousef, J. M. Davis, *Lancet* **1972-II**, 632 (1972).
5. N. Sitaram, A. M. Moore, J. C. Gillin, *Psychiatr. Res.* **1**, 9 (1979).
6. C. Mazure and E. S. Gershon, *Arch. Gen. Psychiatry* **36**, 521 (1979); modified from R. L. Spitzer, J. Endicott, E. Robins, *Research Diagnostic Criteria (RDC) for a Selected Group of Functional Disorders* (Biometrics Research, New York, 1975).
7. All the patients in group 1 were well known to two of the authors (J.I.N. and E.S.G.), who had followed them for more than 6 months in an outpatient lithium maintenance clinic. All patients were functioning adequately, interpersonally and in occupations commensurate with their educational background or as homemakers. During the study one patient became mildly depressed. Among the eight patients in group 2, two could be described as mildly depressed, although they were functioning adequately.
8. A. Rechtschaffen and A. Kales, *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects* (Brain Information Service/Brain Research Institute, Los Angeles, 1968).
9. All subjects were adapted for two nights prior to the infusion studies, except for three patients (group 1) and four normal volunteers on whom we could obtain only one adaptation night. The data from these subjects were, however, no different from data from those who had been adapted for two nights.
10. T. Sagales, S. Erill, E. F. Domino, *Clin. Pharmacol. Ther.* **10**, 522 (1969).
11. Since the first non-REM period of depressed patients is short, we decided to administer our infusions during the second non-REM period. The REM-to-REM intervals and the non-REM periods subsequent to the first have previously been reported to be normal in depressed patients (*1*). To further confirm this result, we compared the second non-REM period of a group of normal subjects used in previous experiments (*2*) (N = 21, mean = 84.7 minutes) with that of 47 patients with primary depressive illness (mean = 81.9 minutes) who had been studied in our laboratory; there was no significant difference.
12. N. Sitaram, R. L. Cohen, A. Rey, D. L. Murphy, J. C. Gillin, unpublished data. Seven depressed patients (five female and two male, age = 26.8 ± 6.1 years) were tested with the 0.5-mg arecoline dose. The inf-REM_2 latency for the depressed patients (10.5 ± 11.1 minutes) was significantly lower than in the normals (37.5 ± 21.9 minutes) ($P < .02$, two-tailed Mann-Whitney U test). All subjects had been drug free for at least 2 weeks before testing.
13. M. Jouvet, in *Cholinergic Mechanisms*, P. G. Waser, Ed. (Raven, New York, 1975), pp. 455–476.
14. J. C. Gillin, W. B. Mendelson, N. Sitaram, R. J. Wyatt, *Ann. Rev. Pharm. Toxicol.* **18**, 563 (1978); A. G. Karczmar, *Brain Acetylcholine and Neuropsychiatric Disease*, K. L. Davis and P. A. Berger, Eds. (Plenum, New York, 1978) pp. 265–310; J. A. Hobson, R. W. McCarley, T. M. McKenna, *Prog. Neurobiol. (N.Y.)* **6**, 155 (1976); G. W. Vogel, *Am. J. Psychiatry* **135**, 1531 (1978).
15. K. L. Davis, P. A. Berger, L. E. Hollister, E. DeFraites, *Arch. Gen. Psychiatry* **35**, 119 (1978); D. S. Janowsky, M. K. El-Jousef, J. M. Davis, H. J. Sekerke, *ibid.* **28**, 542 (1973); K. L. Davis, L. E. Hollister, J. Overall, A. Johnson, K. Train, *Psychopharamcology* **51**, 23 (1976); C. Tamminga, R. C. Smith, S. Chang, J. S. Haraszti, J. M. Davis, *Lancet* **1976-II**, 905 (1976).

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Preschool Programs and Later School Competence of Children from Low-Income Families

Abstract. *At follow-up in 1976, low-income children who had attended infant and preschool programs in the 1960's had significantly higher rates of meeting school requirements than did controls, as measured by lower frequency of placement in special education classes and of being retained in grade (held back).*

Controversy over the effectiveness of preschool programs for low-income children has been extensive. This report evaluates the effectiveness of preschool on the basis of a new specification of a commonly accepted goal, improving later school competence.

Preschool programs for low-income children developed rapidly in the 1960's. Project Head Start, initiated in 1965, signaled a nationwide commitment to such programs. It was designed to improve children's intellectual skills, to foster their emotional and social development, to help meet their health and nutritional needs, and to involve parents and the larger community in those purposes (*1*). The high educational expectations were dampened by evaluations, such as the Westinghouse-Ohio University report, which concluded that preschool did not have a lasting effect on children's intellectual development (*2, 3*). Among social scientists the negative results occasioned a review of the premises of early intervention, a reopening of the nature-nurture controversy, inquiries into the nature and meaning of intelligence testing, and doubts about the role of early experience in later development (*4*).

The research reported here provides evidence of the effectiveness of preschool programs for children from low-income families. [Longer reports are available (*5–7*).] It is based on follow-up of eight separate preschool research projects, and it examines their effects well beyond the primary grades: the median subjects were in the seventh grade.

The research was conducted by members of the Consortium for Longitudinal Studies. Twelve investigators (*8*) who had independently designed and conducted experimental preschool programs in the 1960's pooled their original data and conducted a common follow-up study in 1976–77 of the original participants and control groups. Two consortium members (*9*) who had not conducted preschool programs coordinated the follow-up work.

The original preschool programs were located at 11 urban and rural sites in the Northeast, Southeast, and Midwest. Their delivery systems and curricula varied considerably. Some programs concentrated on home visits to teach mothers how to be more effective teachers of their infants and toddlers; in others, 3- or 4-year-olds were taught in a group setting; others had both center and home-visit components. Curricula in the centers were based on the Bank Street child-development model, on Montessori's methods, on Piagetian theory, on the Bereiter-Engelmann method, and others.

The preschool programs of the consortium investigators were originally designed for both demonstration and research purposes. A subset was designed specifically to answer the question of whether preschool was effective, with random assignment (or a close approximation) of children to treatment (preschool) and control groups. We have designated these as experimental designs. Other programs were designed primarily to answer questions such as which curricula were most effective and what were optimal ages of entry or length of stay in a program. Matched comparison groups were used in those designs; they are here designated quasi-experimental.

Of approximately 2700 subjects and controls in the 11 original projects, 1599, ranging in age from 9 through 19 years, were available on follow-up. They can be generally characterized as blacks (94 percent) from low-income families in which the mothers had completed 10.3 years of education on the average and the average head of household was a semiskilled or unskilled worker. Other characteristics are summarized in Table 1. Five types of follow-up data were collected in a common format: an individually administered intelligence test (Wechsler), school record information, scores on school-administered standardized achievement tests, and interviews with participants and parents (usually the mothers).

To guard against artifactual results due to differences between the programs, the subjects were never pooled into a single sample. In all hypothesis tests treatment children were compared with control children from the same project site; the

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