quantitative differences in pharmacologic actions (*12*). Further studies are also required to determine whether the suppression of rapid eye movements by sedative-hypnotic agents represents a primary inhibition of oculomotor function (*13*) that becomes apparent during REM sleep or whether it reflects instead a specific effect upon phasic REM processes.

The absence of REM rebound after barbiturate withdrawal under the conditions of our studies is paralleled by results of a recent study of the effects of ethyl alcohol on sleep. Gross *et al.* (*14*) found that high dosages (3.2 g per kilogram of body weight per day) of alcohol administered for 4 to 6 days severely depressed REM sleep. Nevertheless, withdrawal led only to a return to baseline levels without significant overshoot. These results call into question the assumption that the high level of REM sleep found in some patients with delirium tremens (*15*) represents a rebound phenomenon. This extraordinarily intense REM activity is perhaps the most striking abnormality of brain physiology apparent in human delirium. It is therefore of interest to determine the factors responsible for its sporadic occurrence.

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6. The following appear to be the crucial reports on which the notion of REM rebound following barbiturate withdrawal is based: I. Oswald and R. G. Priest [*Br. Med. J.* **2**, 1093 (1965)] administered 400 g of amobarbital to two subjects for nine nights, then increased the dosage to 600 mg for nine additional nights. The data were presented in a figure that shows an apparent elevation of percentage of REM sleep, maximal in the first three withdrawal nights. No statistical analysis was presented. In a retrospective analysis of these data, I. Oswald [in J. H. Price, Ed., *Modern Trends in Psychological Medicine* (Butterworths, London, 1970), pp. 53–77] did find significantly less ($P < .001$) eye movement activity in recordings made late in the withdrawal period (considered as baseline) compared to the first and third withdrawal nights for the two subjects. However, no mention is made of "blind" scoring, nor is the reason given for selecting these nights for analysis. Evans *et al.* (*2*) studied two subjects receiving 200 mg of amobarbital for 26 nights and one subject who was already addicted to Tuinal (300 mg each of amobarbital and quinalbarbital). Upon withdrawal, the first two subjects showed higher than baseline percentages of REM sleep, but no statistical comparisons were reported. The third subject showed low values for REM (15 percent) during drug administration; withdrawal led to an increase to values (25 to 30 percent) well within the normal range. A. Kales, T. A. Preston, T. L. Tan, C. Allen [*Arch. Gen. Psychiat.* **23**, 211 (1970)] found neither a significant suppression of REM sleep during drug administration nor rebound after withdrawal with 100 mg of pentobarbital administered for three nights. Nevertheless, they suggested that an "intranight" rebound had occurred, with more REM activity early and less later during the withdrawal nights. Such changes, which would be described more accurately as "redistributions" (*3*) rather than "rebounds," were not statistically documented. Nevertheless, the notion of an intranight REM "rebound" has gained widespread acceptance.
7. A. Kales, J. D. Kales, M. B. Scharf, T. L. Tan, *Arch. Gen. Psychiat.* **23**, 219 (1970); J. D. Kales, A. Kales, E. O. Bixler, E. S. Slye, *Clin. Pharmacol. Ther.* **12**, 691 (1971); A. Kales and M. B. Scharf, in *The Benzodiazepines*, S. Garattini, E. Mussini, L. O. Randall, Eds. (Raven, New York, 1973), pp. 577–598; W. C. Dement, V. P. Zarcone, E. Hoddes, H. Smythe, M. Carskadon, in *ibid.* pp. 599–611. However, one group of investigators believes that benzodiazepine suppression of REM sleep *is* followed by REM rebound (I. Oswald, S. A. Lewis, J. Tagney, H. Firth, I. Haider, in *ibid.*, pp. 613–625).
8. Most of the data in experiment 1 were reported by Feinberg *et al.* (*4*). One subject in experiment 2 omitted his 100-mg dose on the fourth night.
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12. The already extensive literature on sedative-hypnotic agents is not easily interpreted with respect to this question, for few studies report measures of both eye movement activity and stage 4 EEG under the requisite conditions of administration and withdrawal. However, combined data from two studies suggest that this same pattern of effects is found for glutethimide, a hypnotic structurally related to phenobarbital [C. Allen, A. Kales, R. J. Berger, *Psychonomic Sci.* **12**, 329 (1968); L. Goldstein, J. Graedon, D. Willard, F. Goldstein, R. R. Smith, *J. Clin. Pharmacol. New Drugs* **10**, 258 (1970)].
13. For example, a specific effect of barbiturates on oculomotor (midbrain) structures is indicated by the capacity of these drugs to produce nystagmus in normal subjects, to temporarily abolish congenital nystagmus, and to alter the relation between accommodation and convergence.
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16. We have recently found that rate of administration of dextramphetamine is a crucial factor in determining whether REM rebound occurs after its withdrawal (I. Feinberg, S. Hibi, M. Braun, C. Cavness, G. Westerman, A. Small, *Arch. Gen. Psychiat.*, in press). Gross and co-workers (personal communication) recently found blood alcohol levels and amount of baseline stage 4 sleep appear related to the occurrence of elevated REM with alcohol withdrawal.
17. Supported by Veterans Administration research funds and by PHS grant MH17855.

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Firing Patterns of Hypothalamic Supraoptic Neurons during Water Deprivation in Monkeys

Abstract. *Water deprivation in monkeys caused an acceleration of action potential firing of supraoptic neurons, but not of neurons located 2 to 3 millimeters above the hypothalamic supraoptic nucleus. Whereas in the normally hydrated animal only 12 percent of the neuroendocrine cells discharged periodically, the proportion of these periodic bursters increased markedly with increasing plasma osmolarity. This finding suggests that such periodically firing supraoptic neurons are those engaged in active neurohypophyseal hormone secretion.*

Several studies have been concerned with relating the electrophysiological activity of hypothalamic neuroendocrine cells with the amount of hormone released from their axon terminals located in the posterior pituitary lobe. Evidence for a causal relationship between neuronal firing and oxytocin release is available; thus, in lactating rats, an explosive increase in impulse activity of neuroendocrine cells consistently precedes the reflex secretion of oxytocin in response to suckling (*1*). In contrast, results on the correlation between neuronal firing and release of antidiuretic hormone in response to acute osmotic stimulation are less clear (*2*). We therefore studied the firing of supraoptic neuroendocrine cells during a prolonged and powerful osmotic stimulus; a water deprivation experiment was performed in monkeys, during which we noted an

Table 1. Patterns and rates of firing of hypothalamic supraoptic neurons as a function of plasma osmolarity during water deprivation. S.D., standard deviation of the mean. Percentages are shown in parentheses.

Plasma osmolarity (milliosmols/kg)	Number of neurons studied	Pattern of firing			Firing rate (spikes per second)	
		Irregular	Periodic bursting	Continuous	Mean	S.D.
≤ 299	16	14 (88)	2 (12)		1.01	0.79
300 to 309	6	3 (50)	3 (50)		1.84	.55
310 to 319	12	2 (17)	8 (66)	2 (17)	2.41	1.29
320 to 329	2		1 (50)	1 (50)	*	
330 to 339	12		5 (42)	7 (58)	5.28	4.11
≥ 340	23		7 (30)	16 (70)	7.19	4.24

* The individual firing rates of the two neurons were 4.07 and 2.87.

increase in the mean firing rate of neuroendocrine cells, and in the proportion of supraoptic neurons which fire periodically. We propose that enhanced neurohypophyseal hormone release under these experimental conditions is related to this change in action potential frequency and patterning.

Five adult female rhesus monkeys weighing approximately 4.5 kg were conditioned to a primate restraining chair, and to the stimulating and recording setup, in order to avoid later use of an anesthetic. The animals were prepared for unit recording [see (*3*)], which was started at least 7 days after completion of the surgical procedure. Supraoptic neurons were identified by antidromic invasion of their cell body following a stimulus applied to electrodes implanted into the posterior pituitary lobe. Frequency and pattern of firing were analyzed with the help of a PDP 8E computer. The animals initially had free access to UAR monkey chow and tap water; later, drinking water was removed for 5 days (one animal), 6 days (one animal), or 7 days (three animals), and the monkeys received only solid food during this period. They showed no apparent signs of discomfort during or after the experiment. Blood samples were collected daily from a chronic intracardiac cannula.

Following withdrawal of drinking water, plasma osmolarity, plasma NaCl concentration, and hematocrit value rose markedly. The relation between osmolarity and duration of water deprivation was linear, with a slope of 7 milliosmols per kilogram of plasma per day above the control value of 299.0 milliosmols per kilogram (standard deviation, 0.1; $N = 5$). Three to four days after the animals again had access to drinking water, their plasma osmolarity had returned to normal.

Prior to removal of water, supraoptic neurons fired at an average rate of 0.95 per second (S.D., 0.72; $N = 14$). During the course of water deprivation, their mean firing frequency rose significantly, and by the seventh day, it had risen to 8.18 per second (S.D., 4.5; $N = 14$). On the fourth day of rehydration, the mean firing rate had fallen to 0.21 per second (S.D., 0.08; $N = 9$). These changes in firing frequency were apparently restricted to the neuroendocrine cells, since the firing of hypothalamic neurons located 2 to 3 mm above the supraoptic nucleus did not vary significantly during or after water deprivation (Fig. 1).

Recordings were fully analyzed from 71 spontaneously active supraoptic neurons from five animals (*4*). In Fig. 1, right, the mean firing frequency of each neuron is plotted against the plasma osmolarity determined on the same day. Although there is a wide scatter of points, especially with high plasma osmolarities, a significant correlation coefficient ($r = 0.65$) is obtained.

Water deprivation affected also the pattern of discharge of supraoptic neurons (Table 1). With plasma osmolarities below 300 milliosmols per kilogram, most cells discharged irregularly at a slow average rate (type *i* cells), while a small proportion (2/16) displayed periodic bursting; in these type *p* cells, bursts with a mean duration of 4.9 seconds (S.D., 1.7) and an intraburst action potential frequency of 5.9 per second (S.D., 2.1) were followed by

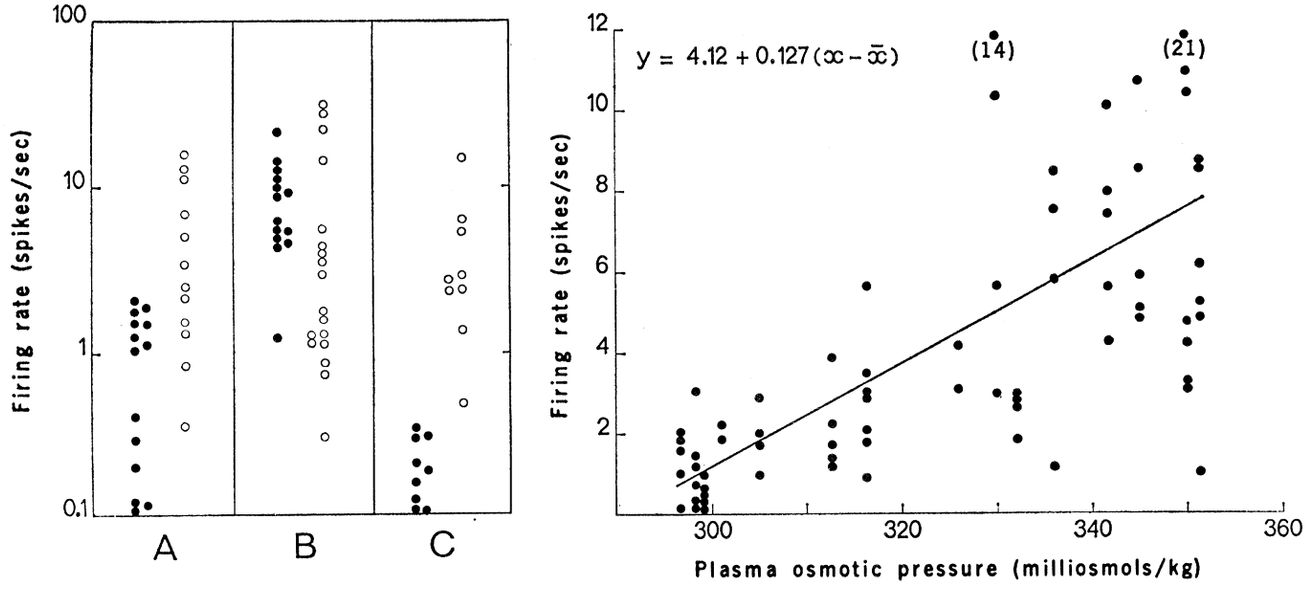

Fig. 1. (Left) Mean firing rates (logarithmic scale) of hypothalamic neurons recorded during the initial control period (A), on the seventh day of water deprivation (B), and on the fourth day of rehydration (C). Supraoptic neuroendocrine cells are shown as closed circles; open circles represent neurons not invaded antidromically and located 2 to 3 mm above the supraoptic nucleus. (Right) Mean firing rate of 71 supraoptic neuroendocrine cells plotted against the plasma osmolarity determined on the same day. The equation of the regression line is indicated above the experimental points; the calculated correlation coefficient equals 0.65.

quiescent periods lasting 10.5 seconds (S.D., 5.8) on the average.

The ratio of type *p* to type *i* cells increased progressively following removal of drinking water. In addition, there was a tendency in type *p* cells for peak firing frequency within bursts and for burst duration (relative to the silent period) to increase during continuing water deprivation. In animals whose plasma osmolarity was higher than 310 milliosmols per kilogram, a firing pattern was encountered in which no periods of cell inactivity occurred, although periodic fluctuations of firing were present occasionally. The relative proportion of these continuously discharging cells (type *c*, mean = 7.80 per second; S.D., 4.11; $N = 26$) increased with further rises in plasma osmolarity (Table 1); by about the same time, the reduction in firing probability which follows antidromic invasion of supraoptic neurons (*5*) is no longer demonstrable (*6*).

The increase in the firing rate of supraoptic neurons observed during chronic water deprivation in monkeys accords well with current views on action potential–secretion coupling in the posterior pituitary lobe (*7*). Moreover, some evidence that a switch from type *i* to type *p* firing is associated with a greater excitatory drive is to be found in the observation that the proportion of periodically discharging neuroendocrine cells increases with increasing plasma osmolarity (Table 1). This contention gains support from the finding that acute stimulation of hypothalamic neuroendocrine cells by suckling (*1*) or by a sudden rise in plasma osmotic pressure (*8*) leads to a biphasic change in membrane excitability characterized by an excitation-inhibition sequence.

There is recent evidence to suggest that the relation between mean firing frequency and amount of hormone released per impulse is not linear. From data on the milk-ejection reflex in the rat, Lincoln (*9*) has calculated that each impulse in a 30-per-second train releases approximately 3 fg of oxytocin; in contrast, each impulse releases 100 to 1000 times less hormone when the same neuroendocrine cells fire at their resting rate of 1 to 2 per second. Electrical stimulation of the supraoptico-neurohypophyseal tract in anesthetized rats (*1*) and rabbits (*10*) is essentially ineffective below about 15 per second, and increases sharply at higher frequencies of stimulation; moreover, it has been shown that rat posterior pituitary lobes kept in vitro release more hormone per impulse the shorter the interval between action potentials (*11*). Since short interspike intervals occur more frequently in type *p* than in type *i* cells, regardless of their average frequency, it is tempting to speculate that type *i* cells contribute little, if at all, to hormone secretion from the posterior lobe, whereas type *p* and type *c* cells are those actively engaged in secretion at the time of recording. Data from Table 1 suggest that, while progressive recruitment of neuroendocrine cells into the actively secreting state occurs when the plasma osmolarity increases to approximately 320 milliosmols per kilogram, additional output of antidiuretic hormone from the posterior pituitary lobe with further increases in osmolarity can be obtained by temporal summation.

A working hypothesis may be that type *p* cells found in control animals in this and in other studies of mammalian hypothalamic neuroendocrine cells (*12*) have a low threshold for osmotic and possibly other types of activation.

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Cerebral Dominance in Musicians and Nonmusicians

Abstract. *Musically experienced listeners recognize simple melodies better in the right ear than the left, while the reverse is true for naive listeners. Hence, contrary to previous reports, music perception supports the hypothesis that the left hemisphere is dominant for analytic processing and the right hemisphere for holistic processing.*

Clinical and experimental evidence suggests that the left hemisphere of the brain is specialized for speech activity and the right hemisphere is specialized for many nonlinguistic functions. Jackson (*1*) related the hemispheric linguistic differences to differences in cognitive activity, suggesting that the left hemisphere is specialized for analytical organization, while the right hemisphere is adapted for direct associations among stimuli and responses. Modern researchers have substantially generalized this differentiation to encompass a wide range of behaviors in normal subjects (*2, 3*).

Experimental (*4–6*) and clinical (*7, 8*) investigators of hemispheric asymmetry appear to agree on the fundamental nature of the processing differences between the two sides of the brain: the left hemisphere is specialized for propositional, analytic, and serial processing of incoming information, while the right hemisphere is more adapted for the perception of appositional, holistic, and synthetic relations.

Up to now, the perception of music has been a well-documented exception to this differentiation. Melodies are composed of an ordered series of pitches, and hence should be processed by the left hemisphere rather than the right. Yet the recognition of simple melodies has been reported to be better in the left ear than the right (*9, 10*). This finding is prima facie evidence against the functional differentiation of the hemispheres proposed by Jackson; rather, it seems to support the view that the hemispheres are special-