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EDITORIAL

Rapid Eye Movement (REM) sleep: cholinergic mechanisms[1]

Otto Loewe conceived of the experiment that led to the discovery of Vagusstoff or acetylcholine during a dream. As this review will attempt to show, it is likely that acetylcholine, acting as a neurotransmitter on a muscarinic synapse within the dorsal tegmentum of the pons, triggered the dream that resulted in its own discovery.

Evidence for the involvement of acetylcholine with Rapid Eye Movement (REM) sleep comes both from human and animal studies. REM sleep is a complicated state, involving, on the psychological level, dreaming, and, on the physiological, activation of the EEG, bursts of rapid eye movements, atonia of the major antigravity muscles, monophasic waves in the pontine, geniculate and occipital areas (PGO spikes), hippocampal theta waves, variability of autonomic functioning, and increased firing rates of most central neurones (with notable exceptions, to be mentioned later). There is also a circadian propensity to REM sleep in man and many mammals. Acetylcholine may be involved in nearly all aspects of REM sleep.

ANIMAL STUDIES

Six different types of data from animal studies suggest that acetylcholine plays an important role in REM sleep.

1. Spontaneous release of acetylcholine

Concentrations of acetylcholine are increased during REM sleep compared with NREM sleep in a cortical cup in the cat (Jasper & Tessier, 1971), in the effluent of the push–pull cannulae in the striatum (Gadea–Ciria *et al.* 1973), and in the ventricles of the dog (Haranth & Venkatakrishna-Bhatt, 1973).

2. Administration of a synthesis inhibitor

Both Hazra (1970) and Domino & Stawiski (1970) found less REM sleep following the administration of hemicholinium, which reduces synthesis of acetylcholine by blocking uptake of choline, the biosynthetic precursor.

3. Administration of pharmacological agonists

Direct application of cholinergic agonists to specific brainstem sites elicits REM or REM-like states. This is true of drugs with mixed muscarinic–nicotinic properties, such as carbachol (George *et al.* 1964; Baxter, 1969; Mitler & Dement, 1974; Van Dongen *et al.* 1978; Velasco *et al.* 1981; Hobson, 1982), relatively pure muscarinic agonists, such as oxotremorine (George *et al.* 1964), bethanacol, or cis-methyl-diaxolane (Hobson, 1982), and acetylcholine itself (Hernandez-Peon *et al.* 1963; Hobson, 1982). The anatomical site is crucial to the physiological state produced. The anterior dorsal pons, such as the fastigial tegmental gigantocellular (FTG) group of cells, has been among the best for eliciting REM-like states, the sublocus coeruleus for inducing atonia, and the posteroventral pontine formation for the evocation of stereotyped eye movements (McGinty & Drucker-Colin, 1982; Hobson, 1982). In some instances, the state produced by cholinergic agonists appears completely normal, except that its duration is prolonged (Hobson, 1982). Interestingly, however, the administration of cholinergic agonists has inhibited REM sleep when given in medulla, midbrain,

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or locus coeruleus (George *et al.* 1964; Masserano & King, 1982; Hobson, 1982; Van Dongen *et al.* 1978). These observations are consistent with the reciprocal interaction model for the control of REM and NREM sleep, which is discussed below (Hobson *et al.* 1976).

4. Administration of cholinesterase inhibitors

Systematically given physostigmine produces prolonged REM periods (Jouvet, 1975) and rapid eye movements, PGO spikes, loss of muscle rigidity, and enhanced firing rates of FTG cells (Pompeiano, 1980) in cats transected at precollicular or retrocollicular levels. Domino *et al.* (1968) induced REM-like states in intact cats with physostigmine and arecoline, a muscarinic agonist. Furthermore, on the basis of studies in reserpinized animals, Karczmar *et al.* (1970) found that physostigmine induced REM sleep and proposed that REM sleep is facilitated as the ratio of cholinergic to aminergic activity increases.

5. Administration of cholinergic antagonists

Atropine and scopolamine delay and reduce the amount of REM sleep in intact and pontine animals (Jouvet, 1975; Domino *et al.* 1968), diminish the number of PGO spikes (Henrickson *et al.* 1972), and block the REM promoting effects of cholinergic agonists and cholinesterase inhibitors (George *et al.* 1964; Domino *et al.* 1968; Jouvet, 1975; Pompeiano, 1980; Hobson, 1982).

6. Electrophysiological and neurophysiological studies

A number of neurones within pontine tegmentum (such as FTG) markedly increase their firing rates during REM sleep (the so-called REM-on cells) and are presumably cholinoreceptive and cholinomimetic (Pompeiano, 1980; Hobson *et al.* 1976; McGinty & Drucker-Colin, 1982). In addition, there are cells which slow their rate or cease firing during REM sleep (the so-called REM-off cells), particularly in dorsal raphe, portions of locus coeruleus, and reticular formation (McGinty & Drucker-Colin, 1982; Pompeiano, 1980; Sakai, 1980; Hobson, 1982). There is no agreement, however, that either of these cell groups or any others are necessary for REM sleep (Jones *et al.* 1977; Sastre *et al.* 1979). Nevertheless, it has been proposed that the cholinergic on-cells and the aminergic off-cells mutually interact: the former are excitatory to themselves and the latter cells; the latter are inhibitory to themselves and to the former (Hobson *et al.* 1976). A mathematical model has been proposed by Hobson *et al.* (1976), based upon the Lotka–Volterra equations, to relate the time course and rate of timing of 'on' and 'off' cells and to account for the oscillation between REM and NREM sleep.

HUMAN CHOLINERGIC STUDIES

Evidence for the cholinergic involvement of REM sleep in man comes from pharmacological studies utilizing receptor blocking agents, cholinesterase inhibitors, and muscarinic agonists. In early studies Toyoda *et al.* (1966) showed that atropine and scopolamine delayed and reduced REM sleep in man. In addition, Sagales *et al.* (1975) showed that tolerance to these REM suppressive effects developed within three consecutive nightly doses of scopolamine.

On the other hand, both physostigmine and arecoline induced REM sleep when administered intravenously to sleeping normal volunteers during either the first or second NREM period (Sitaram & Gillin, 1980). The effects of physostigmine, however, were both time and dose dependent. At lower doses, REM sleep was elicited; at higher doses, wakefulness. The REM periods induced by physostigmine and arecoline were entirely normal in their physiological appearance (EEG, eye movements, atonia, duration). Furthermore, the phenomenology of dreaming appeared completely normal: mental activity recalled from physostigmine induced REM periods was similar to that recalled following awakenings from spontaneous REM periods in terms of being 'dream-like', bizarre, and colourful. Spiegel (1984) has also supported the hypothesis that muscarinic stimulation induces REM sleep by administering RS 86, an experimental muscarinic agonist which shortened REM latency and increased REM sleep in normal volunteers.

As would be expected, scopolamine delayed REM sleep and blocked the REM inducing effects of arecoline (Sitaram & Gillin, 1980). Moreover, the tolerance which Sagales *et al.* (1975) found with three consecutive doses of scopolamine at bedtime may involve the development of muscarinic supersensitivity. To test this hypothesis, scopolamine was administered for three consecutive mornings; by the third night, REM latency (the elapsed time from sleep onset to the first REM period) fell significantly; by the second night of pre-treatment with scopolamine each morning, the REM inducing effects of arecoline were potentiated, which is also consistent with the hypothesis that REM initiation involves a muscarinic synapse and that tolerance to scopolamine may involve muscarinic supersensitivity.

IMPLICATIONS AND APPLICATIONS

1. Psychiatric conditions with short REM latency

Short REM latency (the time between the onset of sleep and the first REM period) has been well documented in patients with major depressive disorders (Kupfer, 1976; Gillin, 1982). It has also been observed in some patients with acute and chronic schizophrenia (Stern *et al.* 1969; Jus *et al.* 1973), anorexia nervosa (Neil *et al.* 1980), obsessive-compulsive disorders (Rapoport *et al.* 1981; Insel *et al.* 1982), and pain syndromes (Blumer *et al.* 1982).

Because short REM latency has been studied so extensively in depression, the following discussion will focus on this aspect. Assuming that REM latency is inversely related to the ratio of cholinergic to monoaminergic activity (see above discussion), then the short REM latency of depression might be consistent with the cholinergic–noradrenergic balance hypothesis of affective disorders originally proposed by Janowsky *et al.* (1972). Direct evidence is lacking for this interpretation of the sleep disturbance of depression, but the following observations are pertinent. First, the sleep changes following the morning administration of scopolamine for three days, described above (Sitaram & Gillin, 1980), mimic those seen in major depression (Gillin *et al.* 1979) – i.e. short REM latency, increased REM density, reduced total sleep time and sleep efficiency. Secondly, patients with major affective illness appear to be unusually sensitive to the REM-inducing effects of arecoline. This has been demonstrated by a technique we have called the Cholinergic REM Induction Test (CRIT) (Sitaram *et al.* 1980, 1982). In this test the elapsed time until the onset of the second REM period is measured, following an infusion of either placebo or arecoline, given 25 minutes following the first REM period. The latency was significantly more rapid after arecoline than after placebo in both depressed patients and controls, but the response was considerably longer in controls than in remitted bipolar patients, patients with anorexia nervosa who were or had been depressed compared with those who were not, patients hospitalized with depression, and in a small number of subjects who presented themselves as normal but who were found to have had a past episode suggestive of depression. Response on the CRIT also appears to be concordant in identical twins (Nurnberger *et al.* 1983). Recently, Berger & Lund (1982) found compatible results, using a modification of the CRIT. Infusing physostigmine (0·5 mg) 5 minutes after sleep onset, they found more awakening in depressives than controls, suggesting an enhanced responsiveness in depressives to cholinergic stimulation. All these findings suggest that the CRIT may be measuring a genetically influenced trait marker for depression. It is possible that depression is associated with a trait-related muscarinic supersensitivity and a state-related aminergic deficiency.

Another application of these concepts and methods might be in the syndromes associated with antidepressant withdrawal, which Dilsaver *et al.* (1983) postulate to be a state of 'cholinergic overdrive'. Not only are depressive symptoms likely to be exacerbated during this period, but levels of REM sleep are high (Gillin, 1982).

2. Narcolepsy

Since short REM latency is a significant feature of narcolepsy, it is not surprising that physostigmine and arecoline precipitate cataplexy (muscle atonia probably related to that seen in REM sleep) in narcoleptic dogs (Delashaw *et al.* 1979). These observations are also consistent with recent findings

of increased numbers of muscarinic receptors in brains from narcoleptic dogs (Boehme *et al.* 1982). Attempts to treat a small number of narcoleptic patients with the anticholinergic drug, trihexyphenidyl, which has potent anticholinergic effects, or to induce narcoleptic symptoms with physostigmine, were unsuccessful but not definitive (Gillin *et al.* 1976).

3. Mechanism of action of antidepressants

Since the antidepressants, with few exceptions, delay the onset of and reduce the amount of REM sleep, it is interesting that both Khazan *et al.* (1967) and Hill *et al.* (1979) showed that physostigmine reversed these REM suppressive effects in animals. This technique provides a functional method for studying the mechanism of action of antidepressants. Preliminary attempts have been made to study physostigmine's effect upon REM sleep in a new antidepressant in man (Ferini-Strambi *et al.* 1983).

4. Myasthenia gravis

Disturbance of cholinergic, nicotinic neuromuscular transmission is thought to underlie the peripheral clinical manifestations of this disease. Central manifestations have also been postulated. Two groups have tried to use EEG sleep studies of the amount and timing of REM sleep to demonstrate central cholinergic abnormalities, but their results have apparently been discrepant. The first, by Papazian (1976), reported decreased and disturbed REM sleep. The second, by Mennuni *et al.* (1983), found decreased REM latency. Further studies are needed to clarify these differing results.

5. Sleep and memory

It has long been hypothesized that REM sleep plays an important role in the consolidation and reorganization of memory. Furthermore, cholinergic mechanisms are also implicated in memory. Studies which tie together these concepts may be of value. On the clinical side, REM sleep is diminished in some children with mental retardation (Castaldo, 1967) and in some patients with Alzheimer's Dementia (Feinberg *et al.* 1967), and it would be interesting to correlate cholinergic deficits and REM sleep in these patients.

6. Poisoning with anticholinesterase agents

In an experimental study of the effects of long-acting cholinesterase inhibitors in volunteers, Bowers *et al.* (1964) reported excessive nightmares and dreaming. Although sleep studies were not performed in that study, Stoyva & Metcalf (1968) observed increased amounts and early onset of REM sleep in farmers exposed to anticholinesterase insecticides.

7. Chronobiology

A number of interesting theoretical models of sleep–wake control mechanisms have recently been proposed (Kronauer *et al.* 1982; Borbeley, 1982). Little is known about the biochemistry or neuropharmacology of circadian systems, but acetylcholine might be involved. Circadian rhythms for muscarinic receptors have been described in autopsy material from human cortex (Perry *et al.* 1977) and from rat brain (Kafka *et al.* 1981). Moreover, Kronauer *et al.* (1982) propose the existence of a 'strong oscillator', termed the 'X oscillator', which regulates the circadian organization of REM sleep, temperature, and cortisol. Since cholinergic agonists lower body temperature and stimulate cortisol secretion, one wonders whether acetylcholine acts upon or through the 'X oscillator'. Zatz & Brownstein (1979) have shown that carbachol administration mimics the effect of light in the rat – i.e. it can phase advance or delay melatonin rhythms, depending upon the circadian phase of administration. This effect, however, appears to be nicotinic rather than muscarinic.

Sitaram & Gillin (1980) have also shown that the ultradian REM-to-REM rhythm in man can be lengthened and shortened by the intravenous administration of scopolamine and arecoline or physostigmine between REM periods, respectively.

DISCUSSION

This review has deliberately emphasized the diverse role of acetylcholine in REM sleep, but is not intended to imply that acetylcholine is the only neurotransmitter involved with REM sleep. In some ways, however, its role is better established than that of other neurotransmitters, such as serotonin and norepinephrine, which may not even be essential to the occurrence of REM sleep. On the other hand, techniques for selective lesioning and mapping of cholinergic neurones in brain have been unavailable until recently and have not been used extensively in sleep studies. Cholinergic neurones are widely distributed throughout the brain, and further studies will be needed to establish whether acetylcholine plays an essential or a modulatory role and how and where it interacts with other neurochemical systems in the physiology of sleep. Then the role of cholinergic mechanisms in both normal and pathological REM sleep may become clearer.

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