α -ADRENERGIC RECEPTOR BLOCKADE INCREASES HUMAN REM SLEEP

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- 1 An α -adrenergic receptor blocking agent, thymoxamine (150 mg i.v.) in the early night sleep of young adults increased REM sleep duration and also brief awakenings in the early night, while slow wave sleep, stage 3 + 4, was diminished. In the later night, however, stage 3 + 4 sleep was increased. Control experiments demonstrated that thymoxamine (i.v.) was without effect on blood pressure.
- 2 REM sleep duration may be inversely proportional to noradrenaline available at central α -adrenoceptors, but the control mechanisms for REM sleep appear interdependent with those for NREM sleep.

Introduction

The possible role of brain amines in sleep has attracted much interest. After imipramine or related compounds such as desipramine (Dunleavy, Brezinová, Oswald, MacLean & Tinker, 1972), or after amphetamine derivatives (Oswald, 1970), rapid eye movement (REM) (paradoxical) sleep is reduced in duration, and intra-sleep restlessness (frequency of transitions into drowsiness or wakefulness) is increased. It is commonly hypothesized that both these groups of drugs increase noradrenaline at post-synaptic receptors, in the one case through reduced re-uptake and in the other through greater release. Consequently, in an earlier experiment, propranolol was investigated, a drug believed to block the action of noradrenaline on β -adrenergic receptors and known readily to enter the brain. An oral dose of 120 mg at bedtime had no effect itself on sleep and did not modify the reduction of REM sleep by imipramine (75 mg) or by dexamphetamine sulphate (10 mg) (Dunleavy, MacLean and Oswald, 1971). We have now investigated an α -adrenergic receptor blocking agent, thymoxamine, administered intravenously.

β -adrenergic receptor blocking agents are used clinically to lower blood pressure. We had no reason to believe thymoxamine would do so in recumbent persons (and no reason to think that change of blood pressure would affect REM sleep) but as a control have conducted a secondary experiment to determine whether thymoxamine could alter blood pressure.

Methods

Ten healthy young adults slept three nights each in the laboratory at approximately weekly intervals, with recording of all-night electroencephalogram (EEG), electro-oculogram (EOG) and submental electromyogram (EMG) at 15 mm/second. A forearm vein catheter was connected with an extension that passed through the bedroom wall. The catheter 6 ml dead space was filled with saline, containing heparin (20,000 i.u./litre). The first night was for adaptation. Saline or thymoxamine was injected on the other two nights, the order being balanced. Five injections were given, at 50 min after first stage 2 sleep onset, and then at 30 min intervals. Injections were of 10 ml, each given during approximately 2 min, either saline with thymoxamine (30 mg) or saline alone.

It was assumed that high blood levels of thymoxamine would exist in the second, third and fourth hours of sleep and, because of pilot experimental results, a specific prediction was made that in these hours enhancement of REM sleep duration would be caused. When recordings were complete the all-night electrophysiological records were coded and scored blind for stages of sleep (Rechtschaffen & Kales, 1968). Raw scores were processed by computer to give amounts and hour by hour distribution of all sleep stages, and episodes of wakefulness.

In order to investigate the blood pressure effect of i.v. thymoxamine (30 mg) in recumbent persons, six healthy young male adults lay for 3 h

Figure 1 Thymoxamine (●) (30 mg $\times$ 5, i.v.) during the early night increases REM sleep duration when compared with saline (○). The results are the mean for ten subjects.

in bed and their blood pressures were recorded every 5 min by clinical sphygmomanometry, to the nearest 5 mm of mercury. After 20 min each was given an i.v. injection of saline (10 ml) into the other forearm and 15 min later a test dose of thymoxamine (15 mg) in saline (10 ml). Then after 25 min the first of four injections of 10 ml at 20 min intervals was given. Two were of thymoxamine (30 mg) in saline (10 ml) and two of saline only. The sequence was ABAB, with three men receiving saline first and three thymoxamine first. The order of injections was not known to the experimenter recording the blood pressure, nor to the subjects.

Results

Three features only of sleep were altered by the thymoxamine injections compared with saline.

REM sleep (Figure 1): in hours 2-4 mean hourly REM sleep on saline nights was 10.5 ± 3.0 min and on thymoxamine nights 17.6 ± 7.6 min (t -test for paired observations, $t = 2.92$, d.f. = 9, $P < 0.01$, 1-tailed). In hours 5-7 REM sleep with saline was 18.5 ± 4.1 min but 15.3 ± 4.7 min with thymoxamine (NS). Stage 3+4 sleep (Figure 2): in hours 2-4 mean hourly stage 3+4 on saline nights was 17.3 ± 6.7 min and on thymoxamine nights 7.6 ± 6.4 min ($t = 3.85$, d.f. = 9, $P < 0.01$, 2-tailed). In hours 5-7 stage 3+4 with saline was 9.0 ± 4.1 min but 12.8 ± 7.6 min with thymoxamine ($t = 2.45$, d.f. = 9, $P < 0.05$, 2-tailed). Sleep was more often punctuated by episodes of wakefulness after thymoxamine and in the time required to

Figure 2 Thymoxamine (●) (30 mg $\times$ 5, i.v.) decreases slow wave sleep stage 3+4, with later apparent compensatory increase when compared with saline (○). The results are the mean for ten subjects.

accumulate the second, third and fourth hours of sleep there intervened a mean hourly 0.3 ± 0.5 min of wakefulness on saline nights but 5.5 ± 7.1 min on thymoxamine nights ($t = 2.26$, d.f. = 9, $P < 0.05$, 2-tailed). In hours 5-7 intervening wakefulness on saline amounted to 1.2 ± 1.2 min, on thymoxamine 0.9 ± 1.9 min (NS).

Apart from the periods of recording clearly classifiable as stage REM there were episodes on some thymoxamine nights of similar appearance except for retention of fairly high muscle tone and relatively sparse eye movements. This anomalous sleep stage was excluded from the above figures but averaged 0.8 min/h in hours 2-4.

Injections of thymoxamine appeared capable of provoking REM periods. Examining sleep cycle durations in terms of the time from the start of the first REM period to the start of the second REM period and then to the start of the third REM period, there were four cycles of between 30-36 min duration on thymoxamine nights and none on saline nights.

The blood pressure data were evaluated by comparing readings associated in time with the thymoxamine (30 mg) injection and those associated with the saline injection. The blood pressure reading just prior to each injection and the three immediately following each injection were selected, the mean of the two instances for each individual obtained, and then the group mean and standard error for each of the four blood pressure values. Figure 3 indicates that there was no difference between the saline and thymoxamine condition. A small rise from the time of the preliminary saline injection may have related to complaints of increasing discomfort from injections into the same arm and often the same vein.

Figure 3 Blood pressures (mean $\pm$ s.e. mean, $n = 6$; $\circ$ systolic; $\bullet$ diastolic) (a) in the early part of the session in relation to the preliminary i.v. saline injection (b) in relation to thymoxamine (30 mg, i.v.) (c) in relation to saline i.v. (administered as often before as after thymoxamine) (d) at 25 and 30 min after the last injection. There is a slight rise overall but no difference between the two principal conditions.

Discussion

The occasional anomalous REM-like sleep, in which muscle tone remained fairly high, has been seen not only in this study but in earlier ones in which drugs affecting brain amines were used (Akindele, Evans & Oswald, 1970; Dunleavy *et al.*, 1972).

Sabelli, Bartizal, Giardina & Myles (1972) found α -adrenergic receptor blocking agents modified cortical visual evoked potentials in rabbits, and Rees, Butler, Gosling & Besser (1970)

found that thymoxamine altered the human pituitary hormone response to methylamphetamine. These observations and our own indicate that thymoxamine acts on the brain, including the human brain, and, by extended inference, that it does so through α -adrenergic receptor blockade (Birmingham & Szolcsányi, 1965).

Our findings cannot be attributed to secondary effects through blood pressure changes and are consistent with beliefs that brain noradrenaline is involved in the regulation of sleep. Hartmann & Schildkraut (1973) proposed an inverse correlation between available brain noradrenaline and REM sleep duration. They pointed out that the amount of noradrenaline in the brain can be reduced either by the administration of α -methylparatyrosine, with concomitant increase of REM sleep duration (Hartmann, Bridwell & Schildkraut, 1971; King & Jewett, 1971; Stern & Morgane, 1973; Wyatt, Chase, Kupfer, Scott, Snyder, Sjoerdsma & Engelman, 1971) or by 6-hydroxydopamine, also with increase of REM sleep (Hartmann, Chung, Draskoczy & Schildkraut, 1971). Using a different method we too have reduced available noradrenaline and, in harmony with the above authors' belief have observed REM sleep enhancement. Specifically our work links REM sleep control to α -adrenergic receptor action but, more widely, suggests interdependent mechanisms for the control of slow wave sleep stages 3 and 4 and of sleep-wakefulness generally.

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References

- AKINDELE, M.O., EVANS, J.I. & OSWALD, I. (1970). Monoamine oxidase inhibitors, sleep and mood. *Electroenceph. clin. Neurophysiol.*, **29**, 47-56.
- BIRMINGHAM, A.T. & SZOLCSÁNYI, J. (1965). Competitive blockade of adrenergic α -receptors and histamine receptors by thymoxamine. *J. Pharm. Pharmacol.*, **17**, 449-458.
- DUNLEAVY, D.L.F., BŘEZINOVÁ, V., OSWALD, I., MACLEAN, A.W. & TINKER, M. (1972). Changes during weeks in effects of tricyclic drugs on the human sleeping brain. *Br. J. Psychiat.*, **120**, 663-672.
- DUNLEAVY, D.L.F., MACLEAN, A.W. & OSWALD, I. (1971). Debrisoquine, guanethidine, propranolol and human sleep. *Psychopharmacologia (Berl.)*, **21**, 101-110.
- HARTMANN, E., BRIDWELL, T.J. & SCHILDKRAUT, J.J. (1971). Alpha-methylparatyrosine and sleep in the rat. *Psychopharmacologia (Berl.)*, **21**, 157-164.
- HARTMANN, E., CHUNG, R., DRASKOCZY, P.R. & SCHILDKRAUT, J.J. (1971). Effects of 6-hydroxydopamine on sleep in the rat. *Nature (Lond.)*, **233**, 425-427.
- HARTMANN, E. & SCHILDKRAUT, J.J. (1973). Desynchronized sleep and MHPG excretion: an inverse correlation. *Brain Res.*, **61**, 412-416.
- KING, C.D. & JEWETT, R.E. (1971). The effects of alpha-methyltyrosine on sleep and brain norepinephrine in cats. *J. Pharmac. exp. Ther.*, **177**, 188-195.
- OSWALD, I. (1970). Effects on sleep of amphetamine and its derivatives. In: *Amphetamines and Related Compounds*, ed. Costa, E. & Garattini, S., pp. 865-871. New York: Raven Press.
- RECHTSCHAFFEN, A. & KALES, A. (1968). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*, U.S. Dept. of HEW, NIH Publication No. 204, Washington, D.C.
- REES, L., BUTLER, P.W.P., GOSLING, C. & BESSER, R.

- G.M. (1970). Adrenergic blockade and the corticosteroid and growth hormone responses to methylamphetamine. *Nature (Lond.)*, **228**, 565-566.
- SABELLI, H.C., BARTIZAL, F., GIARDINA, W.J. & MYLES, S.B. (1972). Effects of α -adrenergic blockers on visual evoked responses in rabbits. *Electroenceph. clin. Neurophysiol.*, **33**, 321-324.
- STERN, W.C. & MORGANE, P.J. (1973). Effects of alpha-methyltyrosine on REM sleep and brain amine levels in the cat. *Biol. Psychiat.*, **6**, 301-306.
- WYATT, R.J., CHASE, T.N. & KUPFER, D.J., SCOTT, J., SNYDER, F., SJOERDSMA, A. & ENGELMAN, K. (1971). Brain catecholamines and human sleep. *Nature (Lond.)*, **233**, 63-65.

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