CATECHOLAMINE MECHANISMS: THEIR PRESUMPTIVE ROLE IN THE GENERATION OF REM SLEEP PGO WAVES

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IT CAN no longer be doubted that the neurochemical processes underlying mammalian sleep and waking behaviour at least partially utilise brainstem monoamine systems. This level of understanding of the role of monoamines in state processes has ultimately been due to the convergent findings of a variety of neurobiological disciplines: neurohistology (DAHLSTROM and FUXE, 1964, 1965; PIN *et al.*, 1968 and JONES, 1969); neuropharmacology (KING, 1972 and JOUVET, 1972); and neurochemistry (see JOUVET, 1972). The undisputed leader in the experimental realm as well as in the theoretical conceptualisation of monamine systems and how they relate to state, is Dr. Michel Jouvet. For over a decade Jouvet and his colleagues in Lyon have steadily marshalled incontrovertable evidence implicating these systems in the state processes. Largely through their efforts the relationships between 5HT and sleep, NE and cortical arousal, and DA and behavioural arousal have given rise to a general construct that might be termed the "monamine theory of state" (JOUVET, 1972). As with other bonafide paradigms that are relatively new and as broad as this, the monoamine theory has been hotly contested and debated throughout its ascendancy. Yet, presently, as a measure of its viability and value, it remains essentially intact despite its rather defiant scope. Whether or not the monoamine construct continues to remain intact as a basic descriptor of state processes in the future is irrelevant to its value as a starting point and impetus for research in the present. Clearly, monoaminergic mechanisms are now among the most vigorously investigated processes in the mammalian brain. Research into these processes has offered the unique opportunity to unify lesion, neuropharmacological, and neurochemical studies in an attempt to describe and analyse the underlying mechanisms of behaviour. Indeed, the interdisciplinary study of state (perhaps the most basic mammalian behaviour) has fostered the concept that monoamines may mediate *specific* waking as well as sleeping sub-processes within the very general concept of states.

With reference to the present catecholamine symposium, Dr. Jouvet has expertly outlined the currently viewed role of these specific monoamines (i.e. NE and DA) in waking phenomenon and REM sleep processes. With reference to the latter, Dr. Jouvet suggests that a noradrenergic mechanism located in the nucleus subcoeruleus is at the basis of the *sine qua non* of feline REM phasic phenomena, the ponto-geniculo-occipital (PGO) wave. The evidence for this suggestion he derived from

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the observation that in cats, both neuropharmacological (6-OH DA) as well as electrolytic lesions in this norepinephrine containing locus result in the long lasting suppression of REM sleep, including the ubiquitous PGO waves. In addition, results from other studies utilising the administration of a variety of other neuropharmacological agents have indirectly implicated noradrenergic mechanisms in the generation of PGO waves (JONES, 1972).

Work in our laboratory at Stanford bears on this specific problem raised by Jouvet and his colleagues: the neurochemical basis of the PGO wave. Our approach to this problem with respect to catecholaminergic (CA) mechanisms has utilised two experimental manipulations in cats: (1) The direct and selective neuropharmacological impairment of CA mechanisms through administration of alphamethyl-p-tyrosine (AMPT); and (2) the administration of CA antagonists secondary to chronic administration of *p*-chlorophenylalanine (PCPA).

STUDIES USING ALPHA-METHYL-*p*-TYROSINE (AMPT)

The CA anti-synthesis agent AMPT induces a severe depletion of brain CA when administered to cats (KING and JEWETT, 1971; HENRIKSEN and DEMENT, 1972). In our hands, AMPT infused by way of an intravenous drip to avoid nephrotoxic side effects, depleted regional brain NE over 70 per cent. This depletion was accompanied by an initial increase (during the first 24 hr following initiation of the drip) in both the per cent REM sleep of total sleep as well as the absolute amount of REM sleep. As administration was contin ed, slow-wave sleep (SWS) time increased dramatically such that at the height of the sleep effects (24—48 hr following initial administration) SWS could itself account for over 60 per cent of the 24 hr recording time. During this peak effect on sleep no change in either the frequency, amplitudes or temporal relationships of the REM PGO waves could be seen (See Fig. 1). On the

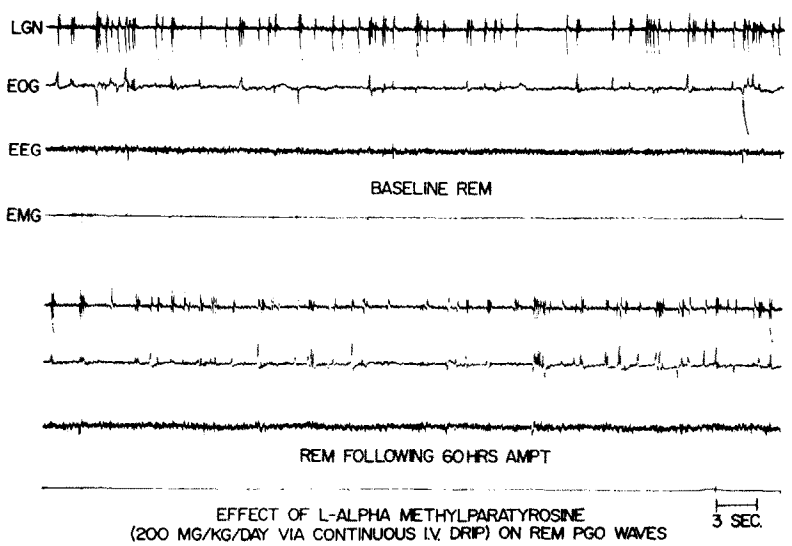


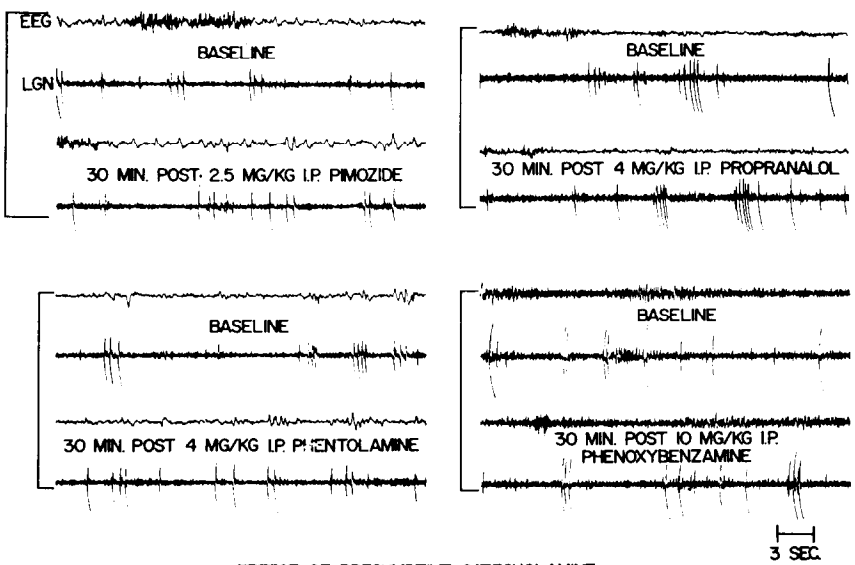
FIG. 1.—The top 4 and bottom 4 polygraphic tracings show approximately 1 min of REM sleep in each case. Note the essentially identical nature of the LGN record. Abbreviations: LGN, lateral geniculate nucleus; EOG electroculogram; EEG, cortical electroencephologram; EMG, neck electromyogram.

other hand, a significant increase in the absolute number of REM PGO waves was seen due to the initial increase in REM sleep time. Similar results, using slightly different experimental procedures have been reported by others (KING, C. and JEWETT, R., 1971).

STUDIES USING ANTI-CA AGENTS SECONDARY TO PCPA TREATMENT

Daily injections of 150 mg/kg PCPA to cats result in the emergence of PGO waves into the waking state by the fourth or fifth treatment day. These waves are by all criteria identical to the PGO waves observed during REM sleep in the same cats (see JACOBS *et al.*, 1973). The emergence of PGO waves into the waking state makes these waves more amenable to study as their occurrence is no longer dependent upon the concomitant appearance of other events (i.e. tonic muscle inhibition) definitive of REM sleep. To this PCPA "preparation" we have administered the following anti-CA agents: the DA receptor blocker—pimozide (2·5–4·0 mg/kg); alpha-CA blocking agents—phentolamine (4·0 mg/kg) and phenoxybenzamine (7·5–10·0 mg/kg); the beta-CA blocking agent—propranolol (4·0 mg/kg) and the CA anti-synthesis agent—AMPT(150 mg/kg i.p., split doses). Figure 2 compares sample baseline waking PGO records with those following the anti-CA agents above. In no case did any of the CA antagonists alter the discharge frequency of waking PGO waves when compared to the baseline PGO rate. When AMPT was administered at the height of the PCPA insomnia (at the maximum point of waking PGO's [PCPA days 4–5]), an *increase* in PGO wave frequency was observed in spite of the partial return of behavioural and electrographic SWS.

These results, although far from definitive, argue against the generation of the PGO waves of REM sleep through the participation of CA mechanisms. On the



EFFECT OF PRESUMPTIVE CATECHOLAMINE RECEPTOR BLOCKERS ON WAKING PGO WAVES

FIG. 2.

contrary these results suggest as other reports have (JALFRE *et al.*, 1972), that CA mechanisms may in fact act to inhibit PGO mechanisms.

Although highly speculative, it is possible that the CA neuronal mechanisms proposed by Dr. Jouvet to be related to electrocortical waking (supported by our results) may themselves directly or indirectly act to regulate pontine areas involved with PGO generation and/or projection.

REFERENCES

DAHLSTROM A. and FUXE K. (1964) *Acta Physiol. Scand.*, **62,** (Suppl.) 232.
DAHLSTROM A. and FUXE K. (1965) *Acta Physiol. Scand.*, **64,** (Suppl.) 247.
HENRIKSEN S. and DEMENT W. (1972) *Sleep Res.*, **1,** 55.
JACOBS B., HENRIKSEN S. and DEMENT W. (1972) *Brain Res.*, **48,** 406–411.
JALFRE M., MONACHON M-A and HAEFELY W. (1972) In: *Proceedings of the First Canadian International Symposium on Sleep* (MCCLURE, D. J., Ed.), pp. 155–185. Roche Scientific Service, Vaudrevil, Quebec.
JONES B. MA Thesis, Lyon: Tixier (1969), 87 pp.
JONES B. (1972) *Brain Res.*, **39,** 121–136.
JOUVET M. (1972) In: *Ergeb. der Physiol.*, volume 64, pp. 166–307, Springer-Verlag, New York.
KING D. and JEWETT R. (1971) *J. Pharmacol. Exp. Ther.*, **177,** 188–194.
PIN C., JONES B. and JOUVET M. (1968) *C.R. Soc. Biol. (Paris)* **162,** 2136–2141.