rat. A similar situation was found with cataleptogenic neuroleptics although at the moment the number of experiments is too small to permit a definite statement to be made.

On the basis of these findings we pose the question as to whether drug-induced catalepsy is connected with enhanced excitability in the negative feedback system of the caudate loop.

Further questions are also raised with respect to the rigor appearing after administration of bulbocapnine and cataleptogenic neuroleptics. HONGO, KUBOTA, and SHIMAZU[22] describe a depression of γ motor activity together with the appearance of both spontaneous spindles and spindles arising from electrical stimulation. On the other hand, STEG[23] and ARVIDSSON et al.[24] found a reduction in the efferent γ activity after the cataleptogens reserpine and haloperidol. Whether the increased excitability of the caudate loop with a depressed efferent γ activity can supply an explanation for the rigor produced after bulbocapnine and neuroleptics must remain an open question, particularly as some investigators were unable to demonstrate a connection between EEG spindles and γ activity[25].

Zusammenfassung. Es wurde bei der Ratte die Wirkung von Bulbocapnin auf die durch elektrische Reizung des N. caudatus ausgelösten Spindeln untersucht. Bulbocapnin bewirkt eine Senkung der Reizschwelle für das Auftreten der Caudatusspindeln und eine starke Zunahme ihrer Spannungsamplitude und Dauer. Die Wirkung wird sowohl im N. caudatus selbst, als auch im Kortex beobachtet. Diese verstärkte Erregbarkeit des N. caudatus geht der bekannten kataleptischen Wirkung von Bulbocapnin zeitlich parallel.

G. STILLE and A. SAYERS

Research Institute, Dr. A. Wander S.A., Berne (Switzerland) 20 June 1967.

[22] T. HONGO, K. KUBOTA and H. SHIMAZU, J. Neurophysiol. *26*, 568 (1963).
[23] G. STEG, Acta physiol. scand. *61*, Suppl. 225 (1964).
[24] J. ARVIDSSON, B.-E. ROOS and G. STEG, Acta physiol. scand. *67*, 398 (1966).
[25] J. S. BUCHWALD and E. ELDRED, Electroenceph. clin. Neurophysiol. *13*, 243 (1961).

Cholinergic Actions Related to Paradoxical Sleep Induction in the Mesencephalic Cat

The so-called paradoxical sleep (para-sleep) in the intact animal is characterized by low-voltage fast waves in the neocortex (EEG), an outburst of spike activity (3–8 c/sec) within the pontine reticular formation (PRF), rapid eye movement and no activity of neck muscle (EMG). In the cat with precollicular decerebration (mesencephalic cat), similar phenomena except for the neocortical EEG were observed[1–5]. This state will be tentatively called 'mesencephalic para-sleep'. In the present study, the authors have examined the relationship between several cholinergic agents and induction of the mesencephalic para-sleep.

Five intact cats with implanted electrodes and 84 acute mesencephalic cats were used. The mesencephalic cat was made by decerebration at the precollicular level with a steel blade under ether anaesthesia. Postoperatively, the animal was placed in an incubator regulated to maintain body temperature between 34 and 37 °C. Polygraphic recordings were made of EEG, neck EMG, eye movement, respiration and heart rate; and behavioural studies were performed. Compounds tested were given i.v. through an implanted cannula (1 mm dia.) into a cephalic vein.

In the mesencephalic cat, spontaneous para-sleep state with a 0.5–12 min (mean, 4.9 min; $n = 104$ in 8 cats) duration appeared usually at intervals of 30 min to 3 h beginning 10 to 25 h postoperatively. In such para-sleep state, as shown in Figure 1 (I), an outburst of spike activity appeared in the PRF accompanied by rapid eye movements and no activity of neck EMG. Similar polygraphic changes (Figure 1, II) of 25 min duration were induced by injection of physostigmine sulphate (0.1 mg/kg) to this preparation after a delay of 1.5 min. The outburst of spike activity in the PRF appeared more regularly than that of spontaneous episode of para-sleep. Usually, para-sleep state following administration of physostigmine (0.1 mg/kg) continued for 2–37 min (mean, 17.5 min; $n = 54$). In 54 (78%) of 69 trials in 20 mesencephalic cats, para-sleep appeared within 10 min after injection of physostigmine (0.1 mg/kg) at about 60 min intervals (Fig. 2, A). In control experiments, para-sleep state with around 5 min duration was observed within 10 min following injection of Ringer's solution in 18 (28%) of 64 trials in 23 mesencephalic cats. The effectiveness of physostigmine in inducing para-sleep within 10 min was significant compared with Ringer's solution ($P < 0.01$). It is to be noted that with a larger amount of physostigmine, a longer period of the mesencephalic para-sleep was observed. For example, a dose of 0.05 mg/kg of physostigmine induced a period lasting only 4–14 min (mean, 10.9 min; $n = 26$); whereas, a dose of 0.2 mg/kg of physostigmine induced a 5–46 min period (mean, 24.5 min; $n = 18$) of para-sleep. These observations indicate that physostigmine plays an active role in the induction of mesencephalic para-sleep.

Atropine sulphate (A.S.) (0.1–0.5 mg/kg i.v.) suppressed the effect of physostigmine (0.1 mg/kg) in inducing para-sleep. After every preceding administration of A.S. (13 trials in 9 cats), the physostigmine injections were applied to the cats with no effect in inducing para-

[1] P. BARD and M. B. MACHT, in *Neurological Basis of Behaviour* (Eds. G. E. W. WOLSTENHOLME and M. O'CONNER; A Ciba Foundation Symposium, Churchill, London 1958), p. 55.
[2] M. JOUVET, Archs ital. Biol. *100*, 125 (1962).
[3] M. MATSUZAKI, H. TAKAGI and T. TOKIZANE, Science *146*, 1328 (1964).
[4] T. TOKIZANE, in *Progress in Brain Research* (Eds. T. TOKIZANE and J. P. SCHADE; Elsevier Publ. Co., Amsterdam 1966), vol. 21 B, p. 230.
[5] M. MATSUZAKI and M. KASAHARA, Proc. Japan Acad. *42*, 989 (1966).

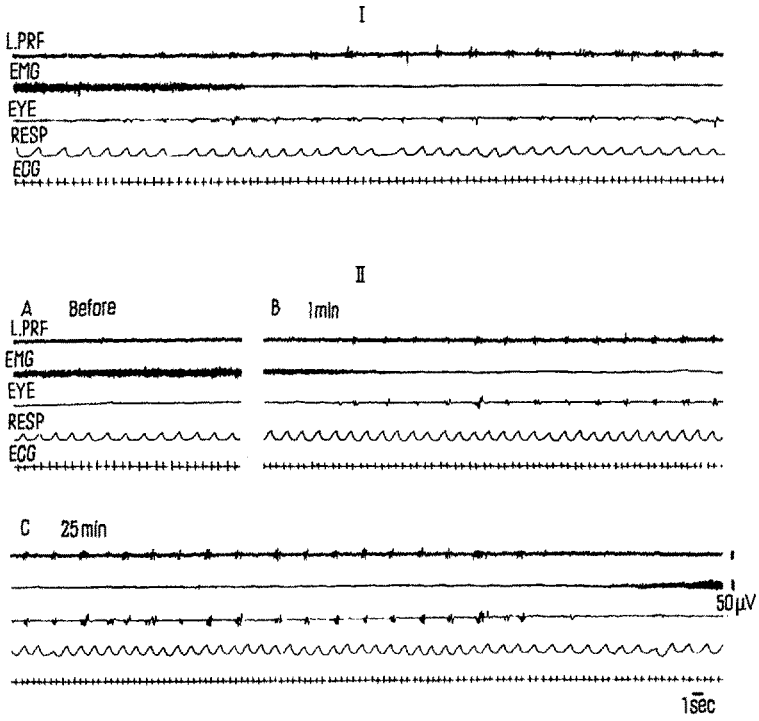

Fig. 1. Polygraphic recordings from a mesencephalic cat in the state of naturally occurring para-sleep (I), and in a similar state occurring after i.v. injection of physostigmine sulphate (0.1 mg/kg) to the same preparation as in I (II). In II (A) is the state before injection, (B) 1 min and (C) 25 min after injection. In each, from top to bottom, EEG from the left pontine reticular formation (L. PRF) by a concentric bipolar electrode, neck muscle activity (EMG), eye movement (EYE), respiration (RESP) and heart rate (ECG) are recorded.

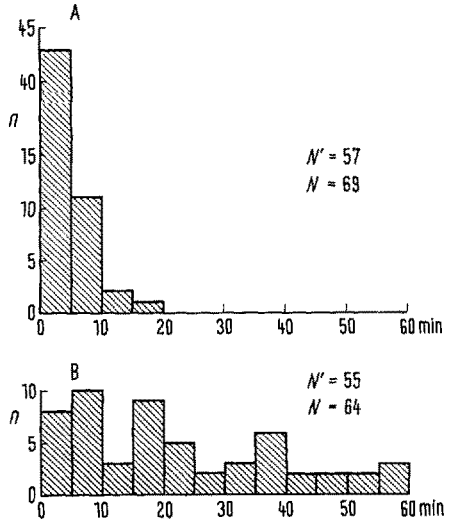

Fig. 2. Frequency histogram of the delay time of para-sleep phase after i.v. administration of physostigmine sulphate (0.1 mg/kg) (A), and of Ringer's solution (B) at 60 min intervals in the mesencephalic cats. The ordinate shows number (n) of para-sleep phases, and abscissae shows the delay time of para-sleep in minutes after injection. N' indicates number of occurrences of para-sleep within 60 min after injection, and N indicates number of injections. (A) was obtained from 20 cats, and (B) was obtained from 23 cats.

sleep. Atropine methylnitrate (A.M.) (0.1–2 mg/kg i.v.; 15 trials in 9 cats) showed no such suppressive effect on the action of physostigmine.

Pilocarpine hydrochloride (0.2 mg/kg i.v.) was also effective in inducing para-sleep in the mesencephalic cats. In 16 (70%) of 23 trials in 10 mesencephalic cats, para-sleep was induced by injection of pilocarpine (0.2 mg/kg i.v.) after a delay of 1–10 min (mean, 3.4 min) and continued for 2–57 min (mean, 11 min; $n = 16$); a dose of 0.1 mg/kg of pilocarpine induced para-sleep in 2 of 9 trials in 5 cats. The i.v. administration of acetylcholine chloride (0.05–1 mg/kg; $n = 7$ in 3 cats), neostigmine methylsulphate (0.05–0.3 mg/kg; $n = 6$ in 3 cats) or bethanechol chloride (0.05–0.1 mg/kg; $n = 6$ in 2 cats) failed to induce para-sleep in the mesencephalic cat, though their peripheral actions (bradycardia, salivation, myosis and vomiting) were observed. These results suggest that the induction of para-sleep by the cholinergic agents is due to their central effects, and not to the peripheral ones[6,7].

In the intact animals, i.v. administration of physostigmine (0.1 mg/kg) evoked arousal or alertness, with appearance of low-voltage fast wave EEG in the neocortex and theta waves in the hippocampus[8].

Para-sleep induction was shown by other cholinesterase inhibitors such as TEPP (0, 0-0′, 0′-tetraethyl pyrophosphate) and DDVP (2, 2-dichlorovinyl phosphate) in the mesencephalic cat[5]. It is probable that the cholinergic mechanism in the central nervous system is involved in inducing para-sleep state in the mesencephalic cat.

Zusammenfassung. In der auf der präcolliculären Höhe dezerbrierten Katze verursacht Physostigmin oder Pilocarpin den sogenannten paradoxen Schlaf. Atropin hemmt diese Einwirkung des Physostigmins.

M. MATSUZAKI, Y. OKADA and S. SHUTO

Department of Neurophysiology, Institute of Brain Research, University of Tokyo (Japan), 20th March 1967.

[6] C. C. PHEIFFER and E. H. TENNEY, Ann. N.Y. Acad. Sci. *66* 753 (1957).
[7] V. G. LONGO, Boll. Soc. ital. Biol. sper. *42*, 97 (1966).
[8] P. B. BRADLEY, in *Reticular Formation of the Brain* (Ed. H. H. JASPER; Little, Brown and Co., Boston 1958), p. 123.