Concerning the Effect of Bulbocapnine on the Caudate Loop

A number of investigations have been made describing the inhibitory effects caused by low frequency stimulation stimulation of the caudate nucleus. Spontaneous motor activity is inhibited to a degree ranging from interruption of current activity to the point of sleep or cataleptic behaviour[1-4]. Suppression of induced cortical effects[5-7] and blockage of learned procedures[8,9] have also been observed. VAN BUREN, LI, and OJEMANN[10] found the so-called arrest response during caudate stimulation in humans.

At the present time it is generally accepted that the caudate nucleus forms part of a negative feedback system receiving inputs from the diffusely projecting thalamus. The modified signals are then fed back to the ventral anterior nucleus of the thalamus and on to the cortex[8]. In this respect the term caudate loop has been used, a neurone circuit apparently controlling not only motoric procedures but also sensory afferents[11-15]. Apparently there is a close correlation between the inhibitory phenomena triggered by caudate stimulation and the spindle groups appearing in the caudate nucleus, thalamus, and cortex after each stimulus impulse. Behavioural changes are caused only with voltages resulting in the appearance of the so-called caudate spindles[8,9] which were first described by SHIMAMOTO and VERZEANO[16]. Single shocks to the caudate nucleus resulted in a response consisting of a variable number of early deflections followed by a relatively quiescent period after which the spindle burst developed as a series of high amplitude oscillations at a frequency of 8–12 c/s[16-20].

The question then arose as to whether certain drugs which cause an akinesia in animals similar to the effect of caudate stimulation, i.e. cataleptogenic compounds, are active on the caudate loop. In an earlier work we had established that no connection exists between the cataleptic effect of drugs and inhibition of the reticular activation system[21]. In the present investigation we examined the effect of the strongly cataleptogenic bulbocapnine on the intensity and release of the caudate spindles.

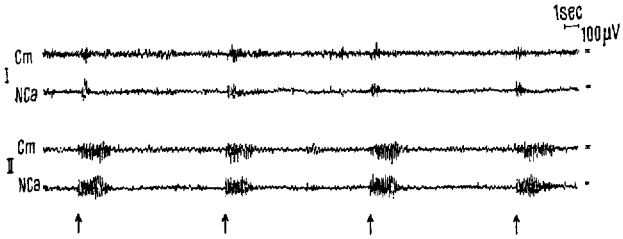
Method. Female rats (Charles River strain) of 230–270 g were used in the current experiments. Bipolar needle electrodes were chronically implanted in the caudate nucleus in each hemisphere and silver leads on the motor cortex using a stereotactic apparatus (C. H. Stoelting Company). An indifferent electrode was mounted in the os frontalis. All the electrodes together with the connecting socket were held in place with Beracryl. The operations were carried out under sodium pentobarbital anaesthesia and at least 3 days were allowed to elapse before the animals were used. Recordings were made on a Schwarzer 12-channel EEG.

The caudate nucleus was stimulated at 10 sec intervals with an impulse of 0.05 msec duration, the voltage varying from 4–8 V (Grass stimulator SC 4 with a stimulus isolation unit 4 B). Bulbocapnine was injected s.c. in doses ranging from 100–150 mg/kg. The spindle threshold was determined before treatment and 30, 60, 120 min etc. after treatment. Following each determination, the degree of catalepsy was also investigated. The animals' forepaws were placed on a 7 cm high column and the time noted during which the animal remained in this unnatural position.

Results. In all of the animals investigated the threshold for the release of spindles by caudate stimulation was lowered following bulbocapnine, i.e. spindles were released by voltages which before treatment were without effect. At the same time the amplitude and duration of the spindle bursts were considerably increased (Figure). Following treatment the electroencephalographic pattern between the spindle groups was conspicuously flat; isolated high amplitude spindles appeared intermittently in the periods between the stimuli. Slow waves were absent and there was no indication that conciousness had been impaired. The bulbocapnine animals showed a complete electrographic response to auditory signals and to electrical stimulation of the mesencephalic reticularis.

The increased spindle excitability ran concurrent with the cataleptic behaviour of the rats.

Conclusions. Following bulbocapnine, spindle groups caused by caudate stimulation are intensified without impairment of excitability of the ascending activation system. This change in caudate loop excitability runs concurrent with the cataleptic behaviour and rigor in the



Rat electroencephalogram from the senso-motoric cortex (Cm) and the caudate nucleus (NCa). Stimulation of the contralateral caudate nucleus with single impulses of 0.05 msec and 8 v at 10 sec intervals. (I) Stimulation spindles before treatment; (II) stimulation spindles 120 min after 130 mg/kg bulbocapnine s.c.

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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.

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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-

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