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The Pineal Gland and Sleep Induction in the Canary

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If canaries have the possibility to choose between light and darkness, a self-selected circadian rhythm of activity and rest can be recorded [Wahlström, 1964]. In most birds the circadian period consists of only one period of activity (light) and one period of rest (darkness). At the start of the period of activity the light is turned on, and this waking-up time is used as a reference point in calculating the circadian period. At the end of

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the period of activity when the bird roosts, the light is again turned off. Studies with a large number of drugs have revealed that the roosting time is easier to influence than the waking-up time. In a recent paper [Wahlström, 1972] the drugs which could induce canaries to roost earlier in this experimental situation were reviewed. Melatonin is one of the most interesting substances studied so far, since it occurs in the body and can induce earlier roosting whenever it is given during the period of activity. Melatonin is almost exclusively synthetized in the pineal gland [Wurtman et al., 1968] due to the specific localization of hydroxyindole-O-methyltransferase (HIOMT), which converts N-acetyllserotonin to melatonin. The pineal gland could thus be of physiological importance with regard to sleep regulation in the canary. In this paper some preliminary data on the effects of two precursors of melatonin (N-acetyllserotonin and 5-hydroxytryptophan [5-HTP]) are reported.

Methods

The method has been described in detail earlier [Wahlström, 1964]. The choice between light and darkness offered to the canary is instrumented through a perch inside the cage. When the bird hops onto this perch the light is extinguished. The light is turned on again when the bird leaves the perch. In each drug experiment a pre-experimental baseline is first established. In the present experiments the average activity, rest and period length from 5 circadian periods were used. During the activity of the following circadian period (circadian period number 0) the drug is given through a stomach tube. The volume administered has been 0.1 ml/10 g. The time of dosage relative to the waking-up time starting circadian period number 0 can be chosen by the experimenter. The changes from the pre-experimental average can then be calculated for several circadian periods.

Results and Discussion

Melatonin can induce canaries to decrease their period of activity (table I). If the drug (1.0 mg/kg) was given early during the activity this decrease in 7 of 12 experiments consisted of a 'nap' which started within 1 h after the melatonin administration [Wahlström, 1971]. Decreased activity was also seen if melatonin was given late in the activity (table I). In these cases, the decreased activity was due to an earlier start of the main rest period. It is inherent in the method that if melatonin is given very late in the period of activity no decrease can be recorded.
Fig. 1. Examples of the pattern of activity and rest in the self-selected circadian rhythm of the canary. At D in the upper panel bird No. 188 received 10 mg/kg 5-HTP by stomach tube. At D in the lower panel bird No. 109 received 2 mg/kg of N-acetylserotonin by stomach tube. Thin line denotes activity (light) and thick line rest (darkness). Distilled water given at unmarked arrows.

Two experiments with the precursors of melatonin have also induced 'naps' similar to those obtained with melatonin. They are shown in figure 1. The bird given 5-hydroxytryptophan (5-HTP) had sporadic 'naps' also in the circadian periods prior to and after the one in which the drug was given, so no certain conclusion regarding a cause-relationship can be drawn. The bird given N-acetylserotonin had no 'naps' for 1.5 months prior to, and 3 months after this experiment. Rest periods ('naps') within the main activity can thus be induced by N-acetylserotonin but are very rare in comparison to the experience after melatonin.

Free Communications: D. Neurophysiology and Neuropharmacology 348

The changes in duration of activity in circadian period number 0 obtained after administration of 5-HTP, N-acetylserotonin and melatonin are given in table I. Since there was no dramatic dose-response in the N-acetylserotonin data, all available experiments with different dose levels have been included. The results must be regarded as preliminary, but it seems as if the pattern of changes induced by 5-HTP and N-acetylserotonin are very similar. Earlier roosting can be induced only during a brief period of sensitivity which occurs when about 30% of the activity period has elapsed (table I).

The following tentative conclusions can be drawn from the present experiments. Melatonin can induce earlier roosting at almost all times during the activity. This means that the sensitivity in the roost-inducing mechanism beyond the process influenced by melatonin does not vary to any large extent during the time period tested. N-acetylserotonin could have a direct or an indirect effect on the inducing mechanism. Since it is a precursor of melatonin, the latter possibility is the more likely. This conclusion is strengthened by the latency seen between administration fairly early in the activity and the effect on the time of roosting several hours later. Latency is also seen in the only experiment in which N-acetylserotonin induced a 'nap' (fig. 1). A step which gives a change in sensitivity in the roost-inducing mechanism has thus probably been introduced between N-acetylserotonin
and melatonin. This could involve the enzymatic conversion of N-acetylserotonin by HIOMT, or some other process, for instance a release. In favour of the latter possibility is the fact that the activity of the enzymes involved in the synthesis of melatonin in other light-active birds (quail and chicken) are highest during darkness in a 12-hour light, 12-hour dark schedule [Bäckström et al., 1972, Pelham and Ralph, 1972], and that the levels of melatonin in the pineal gland of these birds also are highest during darkness [Lynch, 1971]. The fact that the periods of maximal sensitivity to 5-HTP and N-acetylserotonin nearly coincide further indicates that the main effect of 5-HTP in the present experimental situation is due to its precursor status in relation to melatonin. This similarity also makes it unlikely that further regulatory mechanisms with regard to the effects on roosting are involved before the conversion of N-acetylserotonin to melatonin. Whether this mechanism involving melatonin is of physiological significance is a very important question. So far, the negative results obtained in the first preliminary series of pinealectomies in canaries at best keeps the question open [Wahlström, 1972].

Table I. Mean differences (h) between duration of activity in circadian period No. ' 0 9 and a pre-
experimental average2 of activity

Wahlstrom Pineal Gland and Sleep 349

Free Communications: D. Neurophysiology and Neuropharmacology 350

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A Possible Rôle of GABA in the Control of PGO-Wave Activity

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Ponto-geniculo-occipital (PGO) waves disconnected from the sleepwakefulness cycle can be induced in the cat by reserpine [5] which depletes brain catecholamines and 5-hydroxytryptamine (5-HT) as well as by p-chlorophenylalanine (PCPA) [4] which inhibits the synthesis of 5-HT. We are using these drug-induced PGO waves as a pharmacological tool for the investigation of agents and procedures susceptible to interact with the activity of cerebral monoamine neurones (firing rate, transmitter availability and transmitter function) [6]. In previous studies we have obtained evidence for the existence of a 5-HT neurone system exerting a strong inhibitory