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Effect of quinolinic acid on wakefulness and sleep in the rabbit

Short Communication

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Summary. Quinolinic acid (QUIN), an endogenous neuroactive metabolite of tryptophan, administered i.c.v. in doses of 45, 90, 180, and 270 nmol in rabbits, demonstrated an excitatory action on the sleep-wake cycle and behaviour. Doses of 90 and 180 nmol completely abolished the paradoxical sleep phase and induced a 5-fold decrease in the duration of deep slow wave sleep (dSWS) in the first hour of the experiment. Light slow wave sleep (lSWS) duration was not altered. Sniffing behaviour was markedly activated by 180 nmol of QUIN. A dose of 270 nmol completely blocked sleep, diminished the restoration of sleep, induced panic behaviour and, in some animals, induced generalized tonic seizures. Data suggest an excitatory action of QUIN on NMDA receptors involved in the regulation of the sleep-wake cycle in the rabbit.

Keywords: Quinolinic acid, sleep, behaviour, rabbit.

Introduction

Quinolinic acid (QUIN), an endogenous metabolite of tryptophan, has been found in man, rabbit, rat and guinea pig brain (Wolfensberger et al., 1983; Moroni et al., 1984). Its convulsant (Lapin, 1981; Schwarcz et al., 1984), excitant (Stone and Connick, 1985) and neurotoxic (Schwarcz et al., 1983) actions have been demonstrated. Possible pathogenic roles of QUIN in epilepsy (Lapin, 1981; Young et al., 1983; Feldblum et al., 1988), Alzheimer's disease (Moroni et al., 1986) and Huntington's chorea (Schwarcz et al., 1983) have been widely proposed, but contrasting opinions are also known (Reynolds et al., 1988). It is assumed that QUIN can act in the CNS as an endogenous ligand of N-methyl-D-aspartate (NMDA) receptors (Stone and Connick, 1985), which are involved in the regulation of slow wave sleep (SWS) in the rat (Armstrong-James and Fox, 1988).

Until recently the role of metabolites of tryptophan in the regulation of wakefulness and sleep has been discussed mainly in view of the somnogenic action of serotonin (Jouvet, 1969; Spinweber et al., 1983). The above reports support the probable involvement of QUIN in the regulation of wakefulness and sleep. The present paper deals with the action of various doses of QUIN on the temporal structure of the sleep-wake cycle.

Materials and methods

Adult male gray rabbits weighing 2.8–3.3 kg were used. The experimental chamber (50 × 50 × 50 cm) had a balanced suspension clip for EEG wires and a polyethylene injection tube. EEG of the somatosensory cortex was registered using carbon electrodes via epidural leading (Mickiene and Miliauskas, 1976; Roth et al., 1966). A special accelerometer was used to register motility patterns (Mundl and Malmo, 1979). A stainless steel canulla was implanted into the right brain ventricle under barbamylanaesthesia (50 mg/kg, i.v.). Experiments began 10–14 days after surgical procedures. Rabbits received food and water ad lib. until the experiment. Animals were adapted to the experimental conditions over one day.

QUIN was dissolved in saline (pH 4.0) and administered i.c.v. in a volume of 30 µl in doses of 45, 90, 180, and 270 nmol. The rate of injection was 3–4 µl/min. The experiment lasted 3 hr from the onset of drug injection. The same volume of saline with the same pH was used in control. Solutions of QUIN were not titrated to physiological pH because there is no evidence so far in the rabbit for the role of pH of the i.c.v. administered solution of QUIN in its action on the CNS. For the excitant and convulsant effects in the mouse pH is of importance while in the rat it is not (Lapin et al., 1982).

Five behavioral states of an animal were differentiated (Thoman et al., 1979; Zeidner et al., 1983; Pivik et al., 1986), namely active and passive wakefulness (AW and PW), light and deep slow wave sleep (lSWS and dSWS) and paradoxical sleep (PS). Total duration of these states was measured over consecutive intervals of 20 min. These measurements are presented in the paper as mean values of 10 experiments for each dose of QUIN administered to 4–10 rabbits. The total number of animals used was 22. The minimum interval between drug administration was one day. The maximum number of experiments with the same rabbit was three in two rabbits. After the maximum dose of QUIN a rabbit was not used any more. Thus, groups of rabbits used (see Tables 1 and 2) are not homogeneous and identical because some animals were treated with QUIN only once while others were treated two or three times. Due to the neurotoxic action of QUIN the animals treated with QUIN have to be considered as individuals with damaged brain structures (Schwarcz et al., 1983, 1984; El-Defrawy et al., 1986). However, this probable neuronal damage in our experiments (we have no histological information on the brains of rabbits studied) did not disrupt the sleep-wake cycle or EEG parameters measured, as is apparent from the initial normal pre-injection data in all groups of rabbits (Fig. 1), both intact and previously treated. In another animal species, the rat, the repeated administration of QUIN in doses shown to be neurotoxic and causing both unilateral and bilateral degeneration of hippocampal neurons, did not influence any parameter of QUIN-induced seizures (Lapin, 1988). A similar situation seems to exist in our experiments on sleep and wakefulness.

Results

Dose-response and time-response curves of QUIN for mean values of total duration of waking and sleep are presented in Fig. 1. QUIN shortened both phases of sleep and respectively prolonged duration of waking, acting as an

Table 1. Latency of onset of restoration of slow and paradoxical sleep (SWS and PS) in minutes (± S.E.M.) after initial administration of quinolinic acid to the right ventricle of the rabbit brain

Dose nmol	Number of rabbits / Number of experiments	Latency SWS	Latency PS
Control	9/10	16±2 (10)	24±4 (10)
45	6/10	27±5 (10)	57±14 (10)
90	9/10	62±7 (10)	97±6 (8)
180	4/10	55±7 (10)	108±9 (9)
270	10/10	112±15 (3)	− (0)

In parentheses − number of experiments in which restoration was observed in the 3 h period after injection and which were used for the mean evaluation

Table 2. Effect of quinolinic acid on total duration of some states of the sleep-wake cycle (in min) between 20 and 80 min after initial drug adminstration

Dose nmol	Number of rabbits / Number of experiments	AW	PW	lSWS	dSWS	PS
Control	9/10	2.4±0.4	2.6±0.3	2.3±0.4	10.3±0.7	2.5±0.3
45	6/10	5.5±0.7*	5.4±0.9*	2.0±0.2	6.4±1.2*	0.5±0.3*
90	9/10	11.4±2.8*	5.0±1.2	1.6±0.4	1.9±1.3*	0.0
180	4/10	11.0±0.5*	5.4±1.2	1.3±0.6	1.9±1.1*	0.2±0.2*
270	10/10	18.2±0.3*	1.8±0.3	0.0	0.0	0.0

± S.E.M.; * statistically significant difference from control according to Student's t-test at $p \leqslant 0.05$

excitant. The duration of the effect of QUIN depends on the dose used (see Table 1).

Small (45 nmol) and medium (90 and 180 nmol) doses of QUIN blocked both sleep phases during the first hour. Afterwards restoration of the structure of sleep-wakefulness began and it was completed at the end of the second hour of experiment. Duration of the excitant effect of a maximal dose used (270 nmol) was much longer and full restoration had not occurred by the end of the third hour of experiment. This was particularly true for paradoxical sleep restoration of which did not begin during the time of the experiment. Short-lasting (less

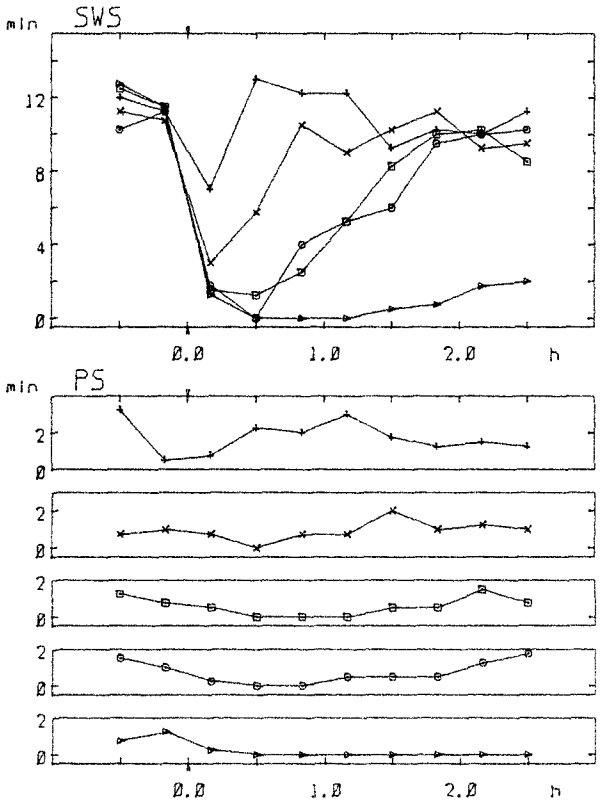

Fig. 1. Dose-response and time-response curves for quinolinic acid (QUIN) for total duration of light and deep slow wave sleep (SWS) and paradoxical sleep (PS). + – control, × – 45, □ – 90, ○ – 180, ▶ – 270 nmol of QUIN. *Ordinate* total duration of sleep phases in 20-minutes intervals (see Methods); *abscissa* time after injection

than 30 min) minimal excitement after i.c.v. administration of saline, which has been described earlier (Schwarcz et al., 1984), was also observed in our experiment. However, this effect disappeared and did not subsequently interfere.

Behaviour of rabbits treated with 45 and 90 nmol QUIN did not substantially differ from controls. During the initial minutes after i.c.v. injection only slightly more frequent breathing and watchfulness were observed. However, marked differences in the sleep-wake cycle are demonstrated even at minimal dose (45 nmol) when redistribution of total duration of both phases of sleep and wakefulness in the first hour after injection occurs. As can be seen from Table 2, this redistribution is demonstrated by a considerable decrease of dSWS and PS and a corresponding increase of AW and PW total durations.

Still more substantial total time redistribution of the same type is observed at 90 and 180 nmol doses of QUIN. It is noteworthy that the total duration of lSWS remains at about control levels for all doses of QUIN, excepting 270 nmol. Table 2 shows that the pattern of the sleep-wake cycle was the same after two medium doses of QUIN, but behavioral alterations appeared only after higher

(180 nmol) doses. Six minutes after injection of 180 nmol QUIN an activation of stereotyped movements was observed, namely rearings, licking and sniffing of the body and sniffing of the chamber. This activated state was evident over 30–40 min and then gradually decreased and disappeared by the end of the second hour of the experiment.

After a dose of 270 nmol QUIN, and in addition to progressing action on states of the sleep-wake cycle (lSWS, dSWS and PS totally disappeared), strong excitement appeared. Panic behaviour, accompanied by midriasis, frequent breathing, tense posture, ataxia, locomotor excitement and rapid arena running were observed for 30–40 min after injection. Arena running continued for 90 min.

In half the animals treated with 270 nmol QUIN tonic seizures appeared 30 min after injection. There were 2–3 attacks with a pause of 2–4 min. Duration of attacks varied between 15 and 30 sec. In all animals marked ataxia was observed for 2 h after seizures. Visually, the rabbits remained excited until the end of the experiment.

Discussion

A dissociated action of QUIN on lSWS and dSWS observed in rabbits in this study appeared to be very similar to that described for N-methyl-D-aspartate (NMDA) in rats (Armstrong-James and Fox, 1988). These authors speculate on the involvement of NMDA receptors in the generation of impulse discharges of somatosensory cortical neurons in rats during SWS. It has been shown that NMDA increased the rate of neuronal discharges and duration of firings, i.e. they occurred more frequently. These effects demonstrate an incresed excitability and a transition from SWS to waking, i.e. the same picture that we observed in our experiments with QUIN. One more similarity in these two studies consists of the resistance of lSWS towards both NMDA and QUIN. Thus our data on the action of QUIN on the sleep-wake cycle agree with the assumption (Stone and Connick, 1985) that QUIN can act as an endogenous ligand of NMDA receptors.

It is noteworthy that similar shortening of SWS and PS has been observed in cats intoxicated by ethanol (Gogichadze et al., 1989). It therefore seems reasonable to speculate that one cannot exclude that this action of ethanol on sleep is mediated, at least partially, through QUIN.

The complex of behavioral effects observed in rabbits treated with the highest dose of QUIN (270 nmol) appeared to be very similar to a so-called "QUIN-syndrome", described in cats after injection of QUIN (500 μg) into the nucleus caudatus (Dutov and Tolpyshev, 1986). This similarity suggests that the nucleus caudatus can be involved in behavioral excitement induced by QUIN in rabbits. The nucleus caudatus has also been demonstrated to be a trigger structure in QUIN-induced seizures in rats (Lapin, 1988).

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