ELECTROENCEPHALOGRAPHIC STUDIES ON MORPHINE
DEPENDENCE IN RABBIT

KIYOMI YAMATSU AND HIROSHI TAKAGI

Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto

Received for publication April 8, 1966

Electrophysiological studies on the drug dependence have been studied by Seevers and Deneau (1) in monkey and by Ishikawa (2) in rabbit.

The experiments reported here were designed to clarify the process of development of tolerance and physical dependence on the morphine using electroencephalographic technique.

Male albino rabbits with chronically implanted electrodes in the hippocampus, posterior hypothalamic area, mesencephalic reticular formation and the motor cortex were used. The changes in coronary dilating action of adenine nucleotides in anesthetized dogs. Therefore further studies were carried out of the effect of MH on the actions of adenosine or adenine nucleotides.

As shown in Fig. 1, coronary dilating action of 3'-AMP was markedly potentiated by the infusion of 0.5 mg/kg/min of MH. On the isolated guinea pig atria, 12.5 µg/ml of MH by which dose showed little effect on the contraction of the atria enhanced markedly the 3'-AMP- or 5'-AMP-induced depressant action (0.5 µg/ml).

The duration of the adenosine-induced heart block in guinea pigs by the method of Rand et al. (4) was prolonged by MH as shown in Table 1. The period of ATP-induced heart block was also prolonged to the same degree by MH. The acetylcholine-induced block which was abolished by atropine, however, was not affected by 2.5 mg/kg of MH. Adenosine deaminase activity in vitro was not influenced by MH as shown in Table 2.

These results show that the potentiation of the coronary dilating and the cardiac action of adenine nucleotides or adenosine by MH is not related to inhibition of adenosine deaminase activity. The mechanism of the potentiation will need further study.

REFERENCES


ELECTROENCEPHALOGRAPHIC STUDIES ON MORPHINE
DEPENDENCE IN RABBIT

KIYOMI YAMATSU AND HIROSHI TAKAGI

Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto

Received for publication April 8, 1966

Electrophysiological studies on the drug dependence have been studied by Seevers and Deneau (1) in monkey and by Ishikawa (2) in rabbit.

The experiments reported here were designed to clarify the process of development of tolerance and physical dependence on the morphine using electroencephalographic technique.

Male albino rabbits with chronically implanted electrodes in the hippocampus, posterior hypothalamic area, mesencephalic reticular formation and the motor cortex were used. The changes in
spontaneous EEG, reticular or hypothalamic arousal response and behavior were used as a measure of development of morphine dependence.

Rabbits were made tolerant to morphine in the following manner: the initial dose of 20 mg/kg by subcutaneous injection, twice daily, was gradually increased to 80 mg/kg, twice daily, in 40 to 50 days.

An intravenous administration of 8 mg/kg of morphine to nontreated rabbits produced a marked reduction in frequency, an increase in amplitude and the frequent occurrence of spindle burst in EEG activity of motor cortex, associated with the irregular slow waves in that of the hippocampus, showing sedative effect. The reticular and hypothalamic arousal responses were suppressed, and the threshold voltage showed an increase of about 30 to 50% at 15 to 30 minutes after injection and lasted more than 3 hours, as shown in Fig. 1-A.

On the other hand, an intravenous administration of 8 mg/kg of morphine to rabbits received the repeated administration of morphine for 3 weeks produced alternately the low voltage fast waves and the high voltage slow waves in the motor cortex from one to 15 minutes after injection, and thereafter the slow waves alone lasted for one to 2 hours. Though animal showed all the while a spontaneous EEG, reticular or hypothalamic arousal response and behavior were used as a measure of development of morphine dependence.

Rabbits were made tolerant to morphine in the following manner: the initial dose of 20 mg/kg by subcutaneous injection, twice daily, was gradually increased to 80 mg/kg, twice daily, in 40 to 50 days.

An intravenous administration of 8 mg/kg of morphine to nontreated rabbits produced a marked reduction in frequency, an increase in amplitude and the frequent occurrence of spindle burst in EEG activity of motor cortex, associated with the irregular slow waves in that of the hippocampus, showing sedative effect. The reticular and hypothalamic arousal responses were suppressed, and the threshold voltage showed an increase of about 30 to 50% at 15 to 30 minutes after injection and lasted more than 3 hours, as shown in Fig. 1-A.

On the other hand, an intravenous administration of 8 mg/kg of morphine to rabbits received the repeated administration of morphine for 3 weeks produced alternately the low voltage fast waves and the high voltage slow waves in the motor cortex from one to 15 minutes after injection, and thereafter the slow waves alone lasted for one to 2 hours. Though animal showed all the while a
state of sedation, the so-called paradoxical sleep pattern which showed the low voltage fast waves pattern in EEG corresponding to the nystagmus, facial muscle twitch and the irregularity of respiratory rhythm in behavior was observed in two cases out of four. The reticular and hypothalamic arousal threshold were not altered or only a few elevated after intravenous administration of 8 mg/kg of morphine, as shown in Fig. 1-A. After 4 weeks, even in doses as high as 12 mg/kg morphine did not produce a marked elevation of EEG arousal threshold, as shown in Fig. 1-B.

Thus, the development of tolerance to suppressive actions of morphine on the ascending reticular activating system and the hypothalamic-hippocampal activating system (3-5) was obviously observed.

In spite of drowsiness in behavior at 16 to 40 hours after the last administration of morphine, the low voltage fast waves in the motor cortex and the regular theta wave in the hippocampus dominated, and these tendency became remarkably in proportion to a period of repeated administration of morphine. However, following withdrawal of morphine injection at 5 to 6 weeks, the arousal pattern in EEG and a state of excitation in behavior were observed. These changes were clearly observed following subcutaneous injection of 20 mg/kg of nalorphine which induced the abstinence syndrome as follows: marked grooming, head twitch, increased motility, hypersensitivity to auditory stimuli and mydriasis etc. These changes are almost in agreement with results of Ishikawa (2) which have observed the changes in spontaneous EEG and behavior following repeated administration of morphine.

The present results indicate that when the change in stimulus threshold at the afferent pathway of the central nervous system is employed as a measure, the time course of development of tolerance to morphine can be shown quantitatively and that electroencephalographic technique is a useful tool for testing morphine dependence in rabbit.

REFERENCES