An Antinicotinic Action of Papaverine in the Central Nervous System

Previous studies from our laboratory, performed on the neuromuscular junction[1,2], taenia coli[3] and ganglionic transmission[4], indicated that papaverine has an antinicotinic effect in the peripheral nervous system. When an adequate and sensitive enough technique was used, it was possible to demonstrate central nervous system effects of papaverine. It was shown that papaverine markedly depressed paradoxical sleep and increased slow-wave sleep in rats[5]. The influence of the cholinergic mechanisms in the brain on the EEG manifestation of sleep have been previously described[6]. These experiments were carried out to demonstrate the antinicotinic action of papaverine in the central nervous system.

Materials and methods. The experiments were performed in the 'encéphalé isolé' preparation of cats of both sexes weighing 2.5–3.5 kg. The technique was essentially similar to that of BREMER[7]. Cannulation of the trachea and transsection of the spinal cord were made under ether anesthesia. After spinal transsection the animals were artificially respired. Epidural needle electrodes were inserted through the skull for bipolar registration of the electrocorticogram. The femoral artery was cannulated for the registration of blood pressure, and the femoral vein for drug injections. Temperature of the animals was controlled by a thermostat and heater.

Results and discussion. The control blood pressure in our experiments had a mean of 82.3 ± 7.5 mm Hg ($\pm$S.E.M.). The administration of papaverine in doses of 5.0 mg/kg decreased blood pressure to 51.7 ± 9.8 mm Hg for 1–3 min. At the same time a homogenous cortical synchronization began, which lasted for 384.5 ± 32.3 sec. Cortical desynchronization was induced in the 'encéphalé isolé' preparations by nicotine, 2-phenyl-3-methyl-tetrahydro-1, 4-oxazinium hydrochloride (Fenmetrazin Spofa) and caffeine respectively. The cortical desynchronization induced by 20 µg/kg of nicotine i.v. in untreated animals lasted 413.7 ± 46.2 sec. The desynchronization induced by nicotine given at 2 h intervals remained relatively stable in control animals. Papaverine pretreatment (5.0 mg/kg) considerably shortened the desynchronization induced by nicotine. The desynchronization was maximally depressed 3 min after papaverine administration to $27.3 \pm 12.4\%$ of the control value. Then the duration of cortical desynchronization gradually returned to the control, reaching $64.9 \pm 9.8\%$ 60 min and $85.8 \pm 11.3\%$ 120 min after papaverine administration (Figure). The cortical desynchronization evoked by i.v. injection of Fenmetrazine (5.0 mg/kg) or caffeine (40 mg/kg) in untreated controls lasted 1290.0 ± 103.4 sec and 883.4 ± 67.8 sec respectively. 3 min after papaverine administration, when the action of nicotine was maximally depressed, the cortical desynchronization evoked by Fenmetrazine and caffeine was not significantly changed, being $95.2 \pm 9.4\%$ and $97.5 \pm 6.1\%$ of controls respectively. Similarly the action of submaximal doses of Fenmetrazine (1.0 mg/kg) and caffeine (15 mg/kg) lasting 482.5 ± 51.4 and 394.3 ± 32.1 sec in untreated controls was only slightly but not significantly shortened to $93.7 \pm 8.6\%$ and $91.3 \pm 10.2\%$ of controls, respectively.

The experiments indicate that papaverine is capable of inhibiting cortical desynchronization induced by nicotine. The inhibition is long lasting and detectable more than 2 h after papaverine administration. In spite of pretreatment with papaverine there were no marked changes in the duration of desynchronization evoked by other stimulants (Fenmetrazine, caffeine) even if they were applied in submaximal doses, evoking cortical desynchronization comparable to that of nicotine. In addition, papaverine induced cortical synchronization lasting several minutes. The close relation of hemodynamic changes to the brain bioelectrical activity has been previously described[8,9]. Similarly it is known that the anticholinergics are able to evoke cortical synchronization[6]. Since the cortical synchronization due to papaverine lasted 2–3 times longer than the lowering of blood pressure, it might be assumed that the cortical synchronization is a result of both the lowering of blood pressure and the anticholinergic action of papaverine. It is suggested that the peripheral antinicotinic properties of papaverine demonstrated on nicotinic receptors in neuromuscular[1,2] and ganglionic[3,4] transmission can also be observed in the central nervous system.

Zusammenfassung. Die Wirkungen von Papaverin auf die kortikale Aktivität des Präparates «encéphalé isolé» der Katzen wurden untersucht. Papaverin rief homogene kortikale Synchronisation für einige Minuten hervor und verminderte kortikale Nikotin-Desynchronisation für einige Stunden.

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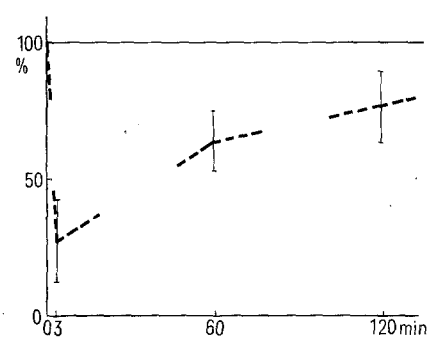

The duration of nicotinic cortical desynchronization after papaverine 5.0 mg/kg pretreatment in 'encéphalé isolé' preparation of the cat. Arithmetic means of 5 experiments are represented with their fiducial limits for P 0.05. 100% = control duration of nicotinic desynchronization.

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