EFFECT OF MORPHINE ON PERMEABILITY OF THE BLOOD-BRAIN BARRIER IN RATS TO NORADRENALIN-H^3

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A single intraperitoneal injection of morphine causes changes in the permeability of the blood-brain barrier (BBB) in rats reflected as a decrease in the passage of DL-7-noradrenalin-H^3 from the blood into the brain. If morphine was injected in a dose of 5 mg/kg the permeability of the BBB was reduced chiefly in the structures of the cortex and medial thalamus, whereas if a dose of 10 mg/kg was given it was also reduced in the region of the hypothalamus and medulla. This effect of a decrease in permeability of the BBB correlates as regards the time of its development with the dynamics of the analgesic effect of morphine.

In modern view the analgesic effect of morphine is accompanied by changes in monoamine metabolism in the CNS [1, 3, 5-8]. Some workers have linked the analgesic effect with the central action of the humoral adrenalin liberated by the action of morphine from the adrenals and penetrating into the brain [4]. In the light of facts already reported it was decided to study the effect of morphine on the penetration of catecholamines injected into the systemic circulation into various brain structures.

The object of the investigation described below was to compare the dynamics of development of the analgesic effect of morphine with its effect on the passage of noradrenalin-H^3 (NA – H^3) from the blood into the brain.

EXPERIMENTAL METHOD

Rats weighing 180-200 g were used in the experiments. Morphine was injected intraperitoneally in doses of 5 and 10 mg/kg. The analgesic effect was assessed from the abolition of the squeaking response arising in rats to compressing the base of the tail with a force of 2.5 kg. The effect of morphine on the permeability of the blood-brain barrier (BBB) was studied by the radioactive isotope method.

DL-7-NA-H^3 (Radiochemical Center, Amersham, England) with a specific activity of 37 mCi/mg was used as the indicator and was injected intravenously in a dose of 6.75 μg/kg, with a radioactivity of 250 μCi/kg. The animals were decapitated 2 min after injection of the isotope and the brain was removed. The sensomotor and parietal regions of the cortex, the medial and lateral thalamus, the hypothalamus, and the medullary reticular formation were taken for investigation. A piece of tissue weighing 10-15 mg was taken from each structure and dissolved in 2 ml 0.5 N KOH solution in a water bath at 60°C. One drop of 30% H_2O_2 solution and 2 ml ethylene glycol were added to each sample. After 30 min 0.4 ml of this solution was mixed with 10 ml of a scintillator prepared with dioxan. The NA-H^3 content in the brain was estimated from the radioactivity of the sample and expressed as the number of pulses per milligram fresh tissue. The Mark I (Nuclear Chicago) scintillation counter was used to measure the radioactivity.

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TABLE 1. Effect of Morphine on Penetration of NA-H^3 into Structures of the Rat's Brain

Dose of morphine (mg/kg)	Analgesic effect (%)	Radioactivity (pulses/min/mg brain tissue)					
		sensomotor cortex	thalamus		hypothalamus	caudate nucleus	medulla
			medial	lateral			
—	0	172 (119—225)	267 (230—304)	210	322 (287—357)	180	146 (115—177)
5	80	102 (87—117)	285 (155—215)	190	285 (248—322)	190	110 (82—138)
10	100	97 (79—115)	158 (131—185)	185	230 (211—249)	170	92 (80—104)

Note. The mean value and its confidence limits are shown.

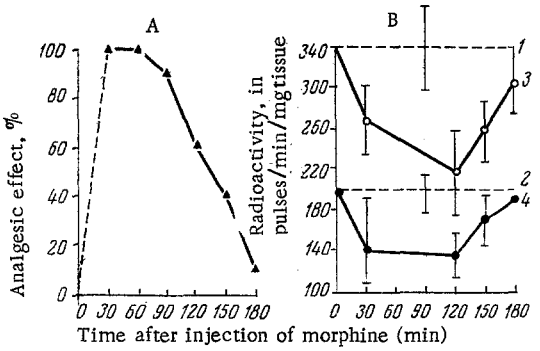

Fig. 1. Analgesic effect and changes in permeability of BBB in rats under the influence of morphine. A) analgesic effect of morphine (10 mg/kg); B) permeability of BBB in region of medial thalamus — 1) control, 3) morphine — and sensomotor cortex — 2) control, 4) morphine.

EXPERIMENTAL RESULTS

Data on the penetration of labeled NA into the various brain structures of the intact rats and of rats receiving morphine 30 min before the isotope are given in Table 1. Special experiments showed that this time interval corresponds to the time of complete development of the analgesic effect of morphine. In a dose of 5 mg/kg morphine inhibited the pain response in 80% of the animals, while if the doses were increased to 10 mg/kg an analgesic effect was observed in all the rats.

It will be clear from the results in Table 1 that the permeability of BBB of the various brain regions for NA—H^3 differs. The radioactivity was highest in the hypothalamus, in agreement with the writers' previous observations [2]; next followed the medial and lateral thalmus, sensomotor cortex, caudate nucleus, and medulla. In a dose of 5 mg/kg morphine appreciably reduced the passage of NA—H^3 from the blood into the structures of the sensomotor cortex (by 41%) and medial thalamus (by 31%). A similar effect was observed in the parietal cortex. In the other regions of the brain the changes in permeability were not statistically significant. With an increase in the dose of morphine to 10 mg/kg a decrease in the permeability of BBB was observed not only in the cortex and medial thalamus, but also in the structures of the hypothalamus (by 29%) and medulla (by 37%). Changes in permeability in the region of the lateral thalamus and caudate nucleus were inconstant.

Analysis of these results suggests that the BBB in the structures of the cortex and medial thalamus is more sensitive to morphine than in the other structures studied — hypothalamus, caudate nucleus, and medulla. It was accordingly interesting to compare the times of development of these changes in BBB permeability with the dynamics of the analgesic effect of morphine in rats. As Fig. 1, shows, the maximum of the analgesic effect occurred 30-90 min after the injection of morphine. At approximately the same times (30-120 min) a decrease in radioactivity was observed in the cerebral cortex. An analgesic effect was observed in 40% of the rats 150 min after the injection of morphine and this corresponded to a persistent decrease in the permeability of BBB which was more marked in the medial thalamus.

The results demonstrate that the analgesic effect of morphine in rats is accompanied by a decrease in the passage of NA—H^3 from the blood into the brain structures. Both effects are increased with an increase in the dose of morphine. Meanwhile the permeability of BBB is reduced not only in the cortex and medial thalamus, but also in the hypothalamus and medulla. It is interesting to note that the analgesic effect and the decrease in the permeability of the BBB in the cortex and medial thalamus develop parallel and largely coincide in time.

The results of these experiments suggest that the decrease in permeability of the BBB of certain brain structures for catecholamines, and perhaps for other substances also, produced by morphine, may play an important role in the mechanism of its analgesic effect.

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