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INDUCTION OF POSTURAL ASYMMETRY BY ENKEPHALIN ANALOGS

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It has recently been shown that opioid peptides methionine- and leucine-enkephalin induce postural asymmetry of the hind limbs in rats with a transected spinal cord [1]. It seems most likely that opiate receptors are involved in the formation of postural asymmetry, for the opiate antagonist naloxone prevents the development of postural asymmetry induced by enkephalins. This paper presents data on the induction of postural asymmetry of the hind limbs in rats by enkephalin analogs.

EXPERIMENTAL METHOD

Male albino rats weighing 150-180 g were used. All operations and measurement of postural asymmetry were carried out under ether anesthesia. The test preparations in aqueous solution, or water alone (control), were injected in a volume of 10 µl suboccipitally into the animals. Laminectomy was performed at the thoracic level 3 h after the injection, and the spinal cord was then divided at the level T6-T7. The presence of postural asymmetry, its magnitude, and the side of the flexed limb were recorded 24 h after injection of the drugs (preliminary experiments showed that by this time the number of animals with postural asym-

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TABLE 1. Induction of Postural Asymmetry by Enkephalin Analogs

Compound	Substance tested	Dose, μg per animal	No. of animals in exp.	No. of animals with postural asymmetry	% of animals with postural asymmetry
1	Control (water)		37	8 $\left(\frac{3}{5}\right)$	22
	Tyr — Gly — Gly — Phe — Leu — Arg	1	7	6 $\left(\frac{2}{4}\right)$	86†
	(Arg^6 — Leu^4 — enkephalin)	10	53	41 $\left(\frac{19}{22}\right)$	70‡
		50	7	4 $\left(\frac{2}{2}\right)$	60
2	Tyr — Gly — Gly — Phe — D — Leu — Arg	1	9	5 $\left(\frac{2}{3}\right)$	55
	(Arg^6 — D — Leu^5 — enkephalin)	50	9	7 $\left(\frac{6}{1}\right)$	77†
3	Tyr — Gly — Gly — Phe — Leu — D — Arg	1	9	4 $\left(\frac{1}{3}\right)$	45
	(D — Arg^6 — Leu^5 — enkephalin)	50	10	7 $\left(\frac{3}{4}\right)$	70*
4	Tyr — Gly — Gly — Phe — Met — Arg	1	10	4 $\left(\frac{3}{1}\right)$	40
	(Arg^6 — Met^5 — enkephalin)	1	10	4 $\left(\frac{2}{2}\right)$	40
5	Phe — Ser — Pro — Phe — Arg	10	14	3 $\left(\frac{2}{1}\right)$	21
6	D — Ala — Gly — Phe — NH_2	10	13	3 $\left(\frac{1}{2}\right)$	23

*P < 0.05.
†P < 0.01.
‡P < 0.001.

Legend. In parentheses: Numerator gives number of animals with flexion of the left limb, denominator the number of animals with flexion of the right limb. Control (receiving water) and experimental (receiving peptides) groups were compared.

TABLE 2. Effect of Nalorphine on Development of Postural Asymmetry Induced by Arg^6-Leu^5-Enkephalin

Experimental conditions	Number of animals	Number of animals with postural asymmetry	% of animals with postural asymmetry
Analog	21	16	76
Analog + nalorphine	21	6	40*

*P < 0.05; experimental (receiving analog and nalorphine) and control (receiving analog) groups were compared.

metry reaches its maximum). It was considered that the animal exhibited postural asymmetry if its magnitude exceeded or was equal to 3 mm, for the magnitude of spontaneous postural asymmetry observed in certain cases (in not more than 10-20% of animals) did not exceed 2 mm in the intact rats. In some experiments 24 h after injection of Arg-Leu^5-enkephalin intraperitoneally into the animals, nalorphine (5 mg/kg body weight) was injected intraperitoneally and postural asymmetry was measured 15 min later. Nalorphine, injected into the animals 24 h after suboccipital injection of water, did not change the number of animals with postural asymmetry. The significance of differences between the numbers of animals with postural asymmetry in the experimental and control groups was estimated by the chi-square test.

EXPERIMENTAL RESULTS

Data on induction of postural asymmetry by enkephalin analogs are given in Table 1. Compounds 1, 2, 3, and 4 caused the development of postural asymmetry of the hind limbs, which decreased in the order 1, 2, 3, and 4. Compounds 5 and 6, which are not structural analogs of opioid peptides, did not change the number of animals with postural asymmetry. The magnitude of postural asymmetry in rats of the control group (receiving water) averaged 3 mm, whereas in the experimental animals (receiving peptides) it averaged 5-7 mm (from 3 to 15 mm). Analog 1, which has been studied more thoroughly than the rest, induced flexion of the left and right hind limbs in an about equal percentage of cases (Table 1).

Nalorphine, an analog of morphine with the properties of an opiate antagonist, if injected 24 h after Arg^6-Leu^5-enkephalin (analog 1), considerably reduced the number of animals with postural asymmetry (Table 2); consequently, opiate receptors were involved in the formation of postural asymmetry. It has been shown that opiate receptors participate in the regulation of motor reflexes at the spinal level [2, 3]. The ability of enkephalin analogs to induce postural asymmetry is perhaps due to differences in the sensitivity of the system regulating activity of symmetrical spinal effector neurons to these analogs. In other words, enkephalin analogs can bring to light the asymmetry of the CNS.

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ROLE OF INFLAMMATION MEDIATORS IN HYPERSENSITIVITY TO STROPHANTHIN ARISING IN SOME TYPES OF EXPERIMENTAL MYOCARDIAL PATHOLOGY

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In acute myocardial ischemia, in inflammation of the heart muscle, and during sensitization by homocardial antigen a decrease in tolerance to cardiac glycosides is observed and may provoke glycoside poisoning [3, 4, 14]. These pathological states are usually accompanied by the accumulation of inflammation mediators in the myocardium [2, 12].

It was accordingly interesting to study the effect of some pharmacological agents which are inflammation mediators on the cardiotoxicity of strophanthin in intact animals, and also to study the effect of antiinflammatory and desensitizing agents on tolerance to strophanthin against the background of the action of these inflammation mediators and after experimental occlusion of the coronary artery.

EXPERIMENTAL METHOD

Experiments were carried out on 312 cats of both sexes weighing 1.9-3.1 kg, anesthetized with pentobarbital sodium (30 mg/kg, intraperitoneally) or thiopental sodium (30 mg/kg, intravenously). The method of estimating the animals' tolerance to strophanthin, based on the values of the minimal arrhythmogenic dose (MAD) and the lethal dose (LD), and also the method

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