NEUROCHEMICAL MECHANISMS OF THE ANALGESIC ACTION OF L-DOPA

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Experimental investigations have demonstrated the great importance of brain adrenergic mechanisms in the regulation of sensitivity to pain [1, 7, 8]. However, the number of drugs which can activate monoaminergic processes in the brain and which are regarded as potential analgesics is restricted to clonidine-like compounds and L-dopa. Whereas the anlgesic effect of clonidine has been proved [1, 7, 11, 14] and is still being actively studied, the few data available on L-dopa are contradictory [12, 13, 15]. This may be due to a large extent to the different assessment of the central action of L-dopa, for most of it is converted in peripheral tissues by the action of dopa-decarboxylase into dopamine [9], which penetrates with difficulty into the brain.

In the investigation described below the effect of L-dopa on behavioral and hemodynamic nociceptive responses was investigated under conditions when peripheral dopa-decarboxylase was inhibited, and the neurochemical and, in particular, the receptor mechanisms of the analgesic effect of the drug were analyzed.

EXPERIMENTAL METHOD

Experiments were carried out on 72 conscious rats. The behavioral components of the nociceptive response were evaluated relative to the latent period of the tail-flick test and the vocalization threshold during electrical stimulation of the tail [2]. Meanwhile the blood pressure (BP) was recorded through catheters implanted chronically into the aorta by means of the VI6-5MA system on a K-121 oscilloscope. L-dopa (Levopa, from KRK, Yugoslavia) was injected in doses of 25 to 300 mg/kg in the form of an aqueous suspension, with the addition of Tween-80. The following neurotropic agents were used for analysis: benserazide (Ro-4-4602, from Roche, USA) in a dose of 50 mg/kg, reserpine (Rausedyl, from Gedeon Richter, Hungary) 5 mg/kg, prazosin (Pratsiol, from Orion, Finland) 1 mg/kg, yohimbine (from Regis, USA) 5 mg/kg, naloxone (Narcan, from Endo Laboratories, USA) 0.1-1 mg/kg, and morphine hydrochloride 2 mg/kg.

TABLE 1. Effect of L-Dopa on BP and Nociceptive Reaction in Rats (M ± m)

Experimental conditions	BP, mm Hg	Nociceptive reaction		
		tail-flick	Electrical stimulation of tail	
		Latent period of tail-flick test, sec	Vocalization threshold, mA	Pressor response of BP, mm Hg
Control	101±11	12,7±1,2	0,55±0,15	28±5
Benserazide (50 mg/kg, 30 min)	106±14	12,7±1,1	0,53±0,19	18±1*
L-dopa (100 mg/kg):				
60 min	97±10	21,7±3,7*	0,87±0,14*	23±2
180 min	99±11	16,5±1,9*	0,70±0,13*	24±3

*P < 0.05 compared with control.

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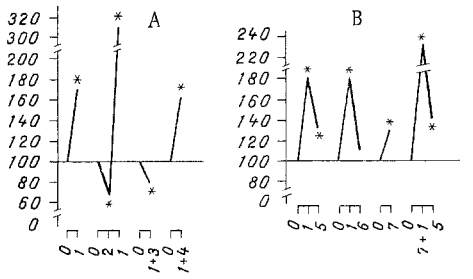

Fig. 1. Results of pharmacologic analysis of adrenergic (A) and opioidergic (B) mechanisms of analgesic action of L-dopa. Abscissa: 0) control; 1) L-dopa (100 mg/kg) preceded by injection of benserazide (50 mg/kg); 2) reserpine (5 mg/kg 24 h before experiment); 3) prazosin (1 mg/kg); 4) yohimbine (5 mg/kg); 5, 6) naloxone (0.1 and 1 mg/kg respectively); 7) morphine (2 mg/kg); ordinate, latent period of tail-flick test during thermal stimulation of rats (in % of initial value). *P < 0.05 compared with control.

EXPERIMENTAL RESULTS

Within the dose range from 25 to 300 mg/kg L-dopa had no analgesic effect, but after preliminary (30 min beforehand) injection of benserazide, it definitely lengthened the latent period of the tail-flick test and raised the vocalization threshold in rats (Table 1). Weakening of the emotional-painful response was not associated with worsening of the animals' functional state, for their spontaneous behavior, their responses to provocative psychogenic factors (grasping with the hand, the loud ringing of a bell) and their systemic BP were virtually unchanged. Against the background of inhibition of emotional-behavioral manifestations of pain, the hemodynamic nociceptive reactions were not significantly reduced (Table 1).

Blockage of dopa-decarboxylase by compounds of the benserazide type, which do not pass through the blood-brain barrier, prevents L-dopa metabolism in the peripheral organs, so that this substance passes into the brain, where it ultimately raises the dopamine and noradrenalin levels [5, 9]. Consequently, the depressant effect of L-dopa on behavioral components of the nociceptive reaction may be due both to its adrenopositive and to its dopamine-positive action. To analyze the monoaminergic mechanism of the analgesic effect of L-dopa, reserpine (5 mg/kg) was injected 24 h before the experiment. As will be clear from Fig. 1A reserpinization, while not changing the dopamine concentration in the brain [4], led to hyperalgesia, which can be explained by noradrenalin deficiency in the brain as a result of exhaustion of its presynaptic reserves. Against this background, under conditions of hypersensitivity of postsynaptic adrenoreceptors, injection of L-dopa induced analgesia; the analgesia, moreover, was more marked than in rats untreated with reserpine. Characteristically, in reserpinized animals which did not receive benserazide, L-dopa did not change sensitivity to pain.

These data are evidence of the central adrenomimetic, and not a dopamine-positive mechanism of the analgesic effect of L-dopa. To discover what kind of adrenergic receptors are involved in the action of this compound, selective blockers of α_1- and β_2-adrenoreceptors were used: prazosin and yohimbine respectively [3, 10] (Fig. 1A). Prazosin completely prevented the analgesic effect of L-dopa. Meanwhile, after administration of yohimbine, the effect of L-dopa develops to the full.

These results not only confirmed our hypothesis of the adrenomimetic nature of the analgesic action of L-dopa, but also led to the conclusion that an important role in the formation of analgesia is played by activation of central adrenergic mechanisms through postsynaptic α_1-adrenoreceptors. In the opinion of several investigators [8, 14, 15], adrenergic processes of regulation of sensitivity to pain may be interconnected with opioidergic analgesic mechanisms. To study the opioidergic component of the action of L-dopa experiments were carried out with naloxone. The results (Fig. 1) showed that naloxone in a dose of 0.1 mg/kg, sufficient to block μ-opiate receptors [6], reduced the analgesic effect of L-dopa by more than half. In a dose of 1 mg/kg naloxone completely abolished the depressant action of L-dopa on emotional-behavioral manifestations of nociceptive reactions.

Demonstration of the opioidergic component in the effect of L-dopa suggested that the compound may potentiate the analgesic effect of opiates. A dose of morphine (2 mg/kg) was

chosen in which the drug caused initial significant inhibition of the tail-flick response. After combined injection of L-dopa and morphine in this dose, the analgesia was greater than the arithmetic sum of the effects of each preparation separately (Fig. 1B). Nevertheless, the question of direct interaction between L-dopa and opiate receptors or of triggering of opioidergic mechanisms through central adrenergic receptors requires further study.

The results were compared with those of a previous study of clonidine [1] and it was concluded that it is activation of central α_1-adrenoreceptors that constitutes the receptor basis of the depressant effect of both these adrenopositive drugs on emotional-behavioral manifestations of pain, although the mechanisms of realization of the effects of these compounds differ significantly. Whereas the action of L-dopa confirms the possibility of synergic functioning of adrenergic and opioidergic analgesic systems, clonidine analgesia is formed independently of opioidergic processes. The ineffectiveness of L-dopa against hemodynamic nociceptive reactions and, at the same time, the definite inhibition of these reactions by clonidine, are evidence in support of the hypothesis [1] that the mechanisms regulating pain components belonging to different modalities are disconnected at the level of the central adrenoreceptors. The "universality" of the pre- and postsynaptic adrenomimetic action of clonidine, which is not characteristic of L-dopa, may perhaps lie at the basis of its ability to inhibit the emotional-behavioral and hemodynamic manifestations of nociceptive reactions simultaneously.

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