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Influence of dopaminergic anti-Parkinsonian agents on inflammatory reactions in rats

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The treatment of Parkinson's disease concerns the metabolism and action of endogenous catecholamines in using L-DOPA and DOPA-decarboxylase/MAO-inhibitors, respectively, or in applying dopamine receptor agonists such as the D_2-agonist bromocriptine. Catecholamines exert acute anti-inflammatory activity [1, 2]. Thus, the question arose whether or not anti-Parkinsonian agents with relation to catecholamine action and metabolism could influence acute inflammatory reactions.

In the present paper we investigated this problem in rat inflammatory models using the serotonin-induced Evan's blue extravasation, the carrageenin paw edema and the primary phase model of adjuvant arthritis. As shown in the Table, dopamine caused a strong anti-inflammatory effect in the Evan's blue extravasation model and produced a moderate and short-lasting inhibition of carrageenin edema. This activity is apparently due to the vasoconstrictor effect of dopamine. L-DOPA and the combination of L-DOPA with the DOPA-decarboxylase inhibitor benserazide caused not any significant influence on the acute inflammatory reactions (Table). Bromocriptine produced a weak to moderate inhibition of carrageenin edema, but it was ineffective in primary adjuvant arthritis (Table).

The involvement of catecholamines in the endogenous anti-inflammatory response to inflammatory stimuli is well known [3, 4]. Chemical sympathectomy by 6-hydroxydopamine caused an increasing of inflammation and, thus it refers to an essential anti-inflammatory effect of endogenous catecholamines [4]. On the other hand, administration of antagonists of adrenergic ß-receptors causes no significant effects in experimental inflammation and the inhibitor of the dopamine ß-hydroxylase, fusaric acid, was likewise inactive [4]. The anti-inflammatory activity of bromocriptine may be due to an interaction with noradrenergic receptors [5] which could cause vasoconstriction. Bromocryptine is also used in galacthorrhoea. Thus, its moderate anti-inflammatory effect could be a useful property in treating galactorrhoea accompanied by proceeding mastitis. Summarizing, the anti-Parkinsonian ergot derivative bromocriptine caused weak to moderate anti-inflammatory effects in acute inflammation whereas the dopamine precursor L-DOPA was completely inactive, also in combination with the DOPA-decarboxylase inhibitor benserazide. Substances with both anti-inflammatory and anti-Parkinsonian effects have already been reported [6, 7].

Table: Influence of the substances tested on inflammation

Substance	Extravasation		Change (%) Carrag. edema		Adjuv. arthr.	
		n	(3 h)	n	(5 d)	n
Dopamine	-82^{++}	8	-36^{+} (1.5 h)	8	n. d.	
L-DOPA	15	12	−4	8		
L-DOPA plus benserazide	1	12			−2	8
Bromocriptine	−17	12	-29^{+}	16	−10	8

+; ++ = $p < 0.05$; 0.01 according to Student's t-test

Experimental

1. Carragenin rat paw edema test

A carrageenin paw edema was induced in female Wistar rats (Barby; Wistar), body weight 100–140 g, according to Winter et al. [8]. Paw volume was determined by a plethysmoscopic device.

2. Rat adjuvant arthritis model

The primary phase of rat adjuvant arthritis was produced by injecting 0.1 ml of Freund's complete adjuvant (Forschungsinstitut für Impfstoffe Dessau Tornau) into the pad of the left hindpaw. The paw swelling was measured by using a sliding calliper.

3. Evan's blue extravasation

Evan's blue extravasation was induced in the back skin of the rats after removing the hairs by means of scissors. The rats were anaesthetized by i.p. 50 mg/kg pentobarbitone (Spofa, Prague); 0.5 ml/100 g body weight of 1% Evan's blue solution (Reanal, Budapest) were i.v. injected via a tail vein; 0.5 µg of serotonin as serotonin-creatinine sulphate (Reanal, Budapest) were intradermally injected in 50 µl isotonic saline (pH of this solution = 5.4), containing the substance, at 4 places; that means two places at each site of the backbone; 15 min after provoking the dye extravasation, the animals were killed by cervical dislocation, the dorsal skin was removed and circular pieces of 10 mm in diameter were punched out at the sites of dye extravasation. Evan's blue elution was performed in 5 ml dimethylformamide for each piece during 24 h at room temperature. The determination of Evan's blue was performed spectrophotometrically at 607 nm.

4. Drugs and dosage

Substances employed: Bromocriptine (Pravidel®; Sandoz AG, Nürnberg); L-DOPA (Dopaflex®, EGIS, Budapest); L-DOPA + benserazide (Madopar®, Hoffmann-La Roche AG, Grenzach-Wyhlen); dopamine (ampoules, VEB Arzneimittelwerk Dresden).

Evan's blue extravasation; the substances were locally injected together with 5-hydroxytryptamine/serotonin): dopamine 10 µg; L-DOPA 1 mg; L-DOPA + benserazide: 1 mg + 0.25 mg; bromicriptine 0.5 mg.

Carrageenin edema: dopamine 2 × 1.0 mg/kg s.c. at hours 0 and 1; L-DOPA 250 mg/kg p.o., L-DOPA + benserazide: 250 + 62.5 mg/kg p.o., bromocriptine 20 mg/kg p.o.

Adjuvant arthritis: the same doses as in carrageenin edema were administered from day 1 until day 4, once daily p.o.

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