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EFFECT OF 6-HYDROXYDOPAMINE ON BLOOD VESSEL REACTIVITY IN THE ISOLATED PERFUSED HIND LEG OF RAT WITH ADJUVANT ARTHRITIS

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ABSTRACT

Catecholamines, essential in stress responses, also modulate inflammatory processes. The synthetic organic compound 6-hydroxydopamine (6-OHDA) can modify the time course of swelling and the exudate volume for carrageenan paw oedema and adjuvant arthritis in rat models. In this study, the effects of 6-OHDA treatment on the vasoreactivity to noradrenaline were investigated using standard and adjuvant arthritic rat models of acute and chronic inflammation. Blood vessel reactivity was tested at different time frames following 6-OHDA and adjuvant injections, with differences seen in vasoreactivity in the isolated perfused hind leg of rats with adjuvant arthritis compared with normal rats, with the maximum vasopressor response to noradrenaline, EAm, successively becoming reduced after the acute phase in the days following injection. The simultaneous injection of 6-OHDA with Freund's complete adjuvant (FCA) caused increased paw swelling in the primary phase of arthritis. An injection of 6-OHDA in the paw of normal non-arthritic rats was associated to a decrease in EAm and an increase in pD2 for noradrenaline, up to day 5 following the 6-OHDA injection; EAm slightly increased, and pD2 decreased in the days leading to day 12 after the 6-OHDA injection. It was also observed that a 6-OHDA injection into the same rat paw 5 days before the FCA injection resulted in increased EAm in the isolated perfused hind leg from days 3 to 5 of arthritis. Arthritis strength significantly increased on days 3 and 5 of arthritis when 6-OHDA had simultaneously been injected with FCA, and on day 7, this effect disappeared. In this paper, we report that 6-OHDA injection increases paw swelling in a time-dependent manner and that adjuvant arthritis changes vasoreactivity compared to normal non-arthritic rats.

KEYWORDS: *6-OHDA, arthritis, catecholamines, inflammation, vasoreactivity*

INTRODUCTION

It has been shown that catecholamines play an important role in the modulation of inflammatory processes (1-2) and that 6-hydroxydopamine (6-OHDA) can modify the time course of swelling of both the carrageenin paw oedema and the effect of adjuvant arthritis, as well as of the exudate volume. Furthermore, both local and systemic vasoreactivity

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to noradrenaline has been proven to be reduced in anaphylactic (3), dextran, and carrageenin paw edema, as well as in adjuvant arthritic rats (4).
In this paper, we investigate the influence of 6-OHDA treatment on the vasoreactivity to noradrenaline in normal and adjuvant arthritic rats to elucidate the role of catecholamines in inflammation.

MATERIALS AND METHODS

In this study, male rats (140-180g) of an outbred Wistar strain were used, and arthritis was induced by subplantar injection of 0.1 ml of Freund's complete adjuvant (FCA) into the right hind paw. The strength of arthritis was recorded by a plethysmometer and a sliding calliper and was recorded visually by a score using strength and frequency of paw swelling and visible secondary lesions as the parameters. In addition, blood vessel reactivity to noradrenaline was tested at different times after adjuvant and 6-OHDA injection, respectively, in the isolated perfused hind leg and paw diameter was measured.

RESULTS

According to Fig. 1, arthritis strength was significantly increased on days 3 and 5 of arthritis when 6-OHDA (60μg per paw) had simultaneously been injected with FCA; this could mean that catecholamines normally act as inflammatory inhibitors after FCA injection at the beginning of arthritis. These effects were not seen after the 6-OHDA sympathectomy, resulting in increased paw volume.

On day 7, the 6-OHDA effect disappeared (Fig. 1); however, in some experiments, increases of the secondary phase of arthritis were also seen (4).

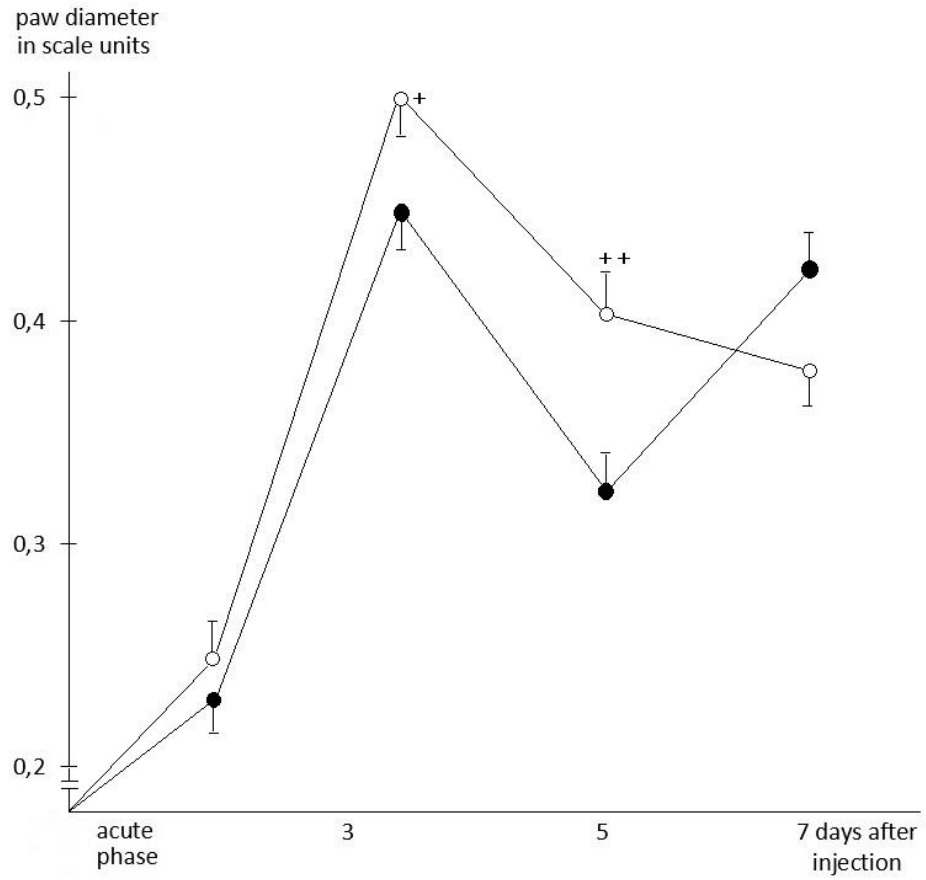

Fig. 1. *The paw diameter was calculated in scale units starting from day 1 at intervals of 3, 5, and 7. The maximum diameters for both adjuvant arthritis rats without and after administration of 6-OHDA at 60 μg /0.1ml were found at day 3. Mean paw swelling of adjuvant arthritic rats without (-●-) and after (-o-) simultaneous administration of 6-OHDA (60 μg/0.1 ml FCA). +, ++ means with p≤ 0.05 and 0.01 statistically different from arthritic controls; n=9-14.*

Blood vessel reactivity in adjuvant arthritis is characterized by a practically unchanged (Table 1), or even slightly increased, resting perfusion pressure, by a decrease of maximum vasopressor effect, E_{Am}, to noradrenaline, and by an increase of the pD_2 value (5).

When 6-OHDA had simultaneously been injected with FCA, resting perfusion pressure remained widely unchanged, whereas E_{Am} was further decreased compared with arthritic rats (Table I).

Table I. *Resting perfusion pressure p_1 (mm Hg, or torr, which is 1 torr=mm Hg, pressure unit) as well as E_{Am} (mm Hg) and pD_2 value of noradrenaline in the isolated perfused hind leg of arthritic rats without and with simultaneous administration of 6-OHDA at different times. +,++ means p= 0.05 and 0.01, respectively, statistically different from arthritic controls; data is given as x ± SD.*

parameter	normal animals	arthritic animals without 6-OHDA			with 6-OHDA		
	n= 34	0.-3. d n= 9	5.-7. d n= 12	14.-16. d n=9	0.-3. d n= 14	5.-7. d n=13	14.-16. d n= 9
P_1	51± 15	42± 8	42± 13	46± 9	53± 15	57± 13	37± 10
E_{Am}	174± 27	167± 54	151± 21	114± 41	120± 32	138± 32	108± 33
pD_2	3.82± 0.55	3.77± 0.16	4.09± 0.30	4.41± 0.26	4.11± 0.31	4.05± 0.26	4.41± 0.39

It seems that vasoreactivity is impaired by mediators of the inflammatory process. After 6-OHDA injection, impairment of vasoreactivity intensifies and, thus, the E_{Am} of noradrenaline further decreases. The pD_2 value is increased after 6-OHDA treatment but only in the early phase of arthritis (Table I); this could be connected with the intensification of the paw swelling in the early phase after simultaneous injection of FCA and 6-OHDA (Fig. 1).

In normal non-arthritic rats, 6-OHDA treatment likewise resulted in an increase of pD_2 up to day 5 after 6-OHDA injection, but then pD_2 was decreased (Fig. 2).

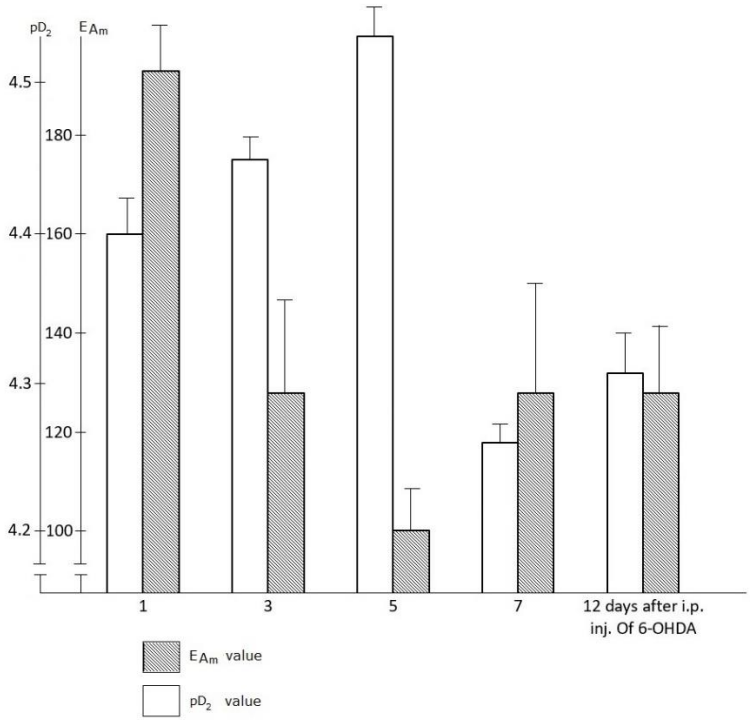

Fig. 2. *E_{Am} (mm Hg) and pD_2 value of noradrenaline in non-arthritic normal rats with 6-OHDA treatment; n=6-7; data is given as x± s.*

On the other hand, E_{Am} successively decreased up to day 5 after 6-OHDA injection and then remained on this low level up to day 12 (Fig. 2). It would be of interest whether an increase of E_{Am} can be expected after this time as a consequence of the sensitization of blood vessel muscles by chemical denervation with 6-OHDA.

Finally, we investigated whether 6-OHDA pretreatment of rats 5 days before FCA injection influences the development of the arthritis and, particularly, the parameters determined in the isolated perfused hind leg. Contrary to the rats with simultaneous 6-OHDA and FCA injection (Table 1), E_{Am} was actually decreased on day 3 of the arthritis (day 8 after 6-OHDA injection) but then was found to be significantly increased on day 5 (Fig. 3).

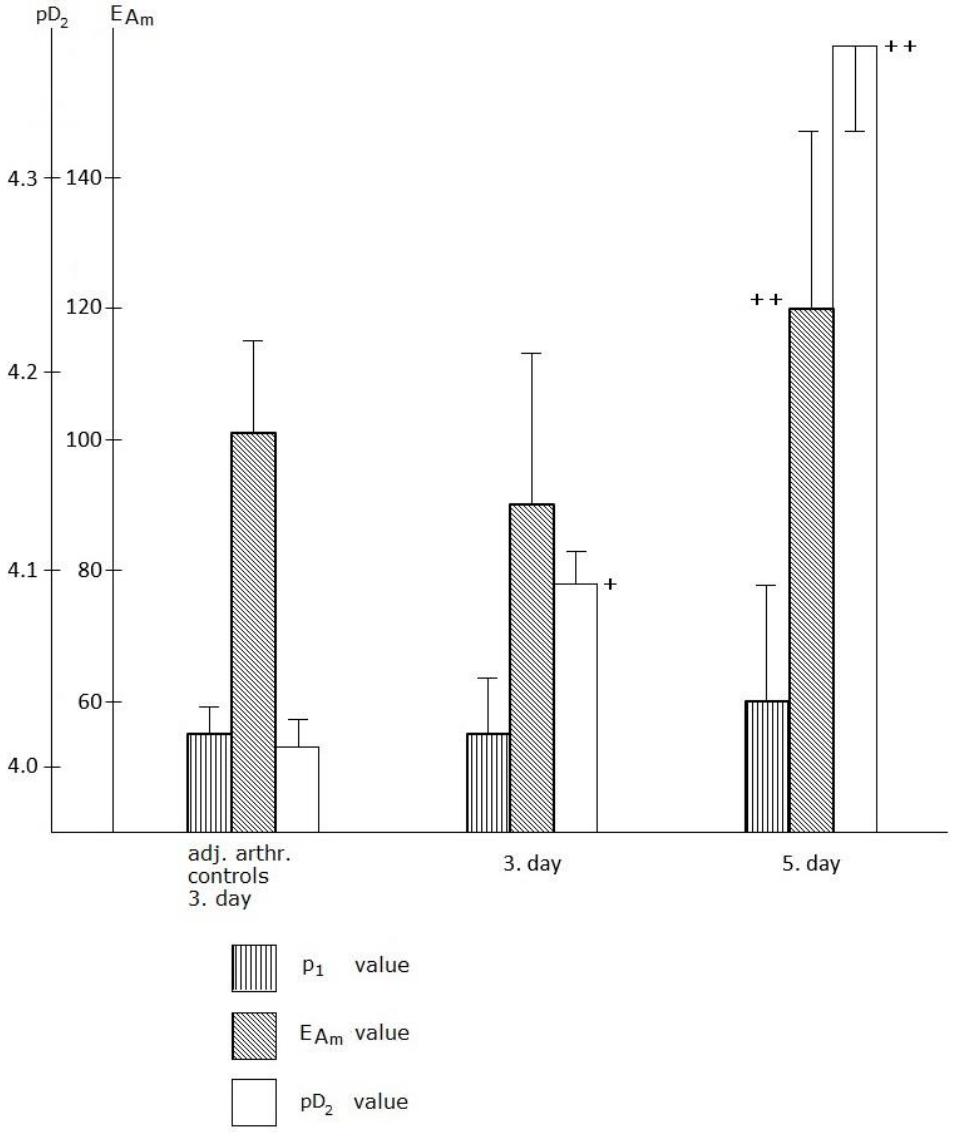

Fig. 3. *Resting perfusion pressure p_1 (mm Hg), E_{Am} (mm Hg), as well as pD_2 value of noradrenaline in arthritic rats (days 3 and 5) after pretreatment with 6-OHDA. +, ++ means with p=0.05 and 0.01 statistically different from arthritic controls; n= 8-16.*

The pD_2 value likewise increased in rats with simultaneous 6-OHDA injection (Table 1) and in normal rats with 6-OHDA injection (Fig. 2) in the early phase. Resting perfusion pressure remained practically unchanged. No explanation can be given for the increase of E_{Am} in arthritic rats given 6-OHDA 5 days before FCA injection.

DISCUSSION

Vasoreactivity was changed in the isolated perfused hind leg of rats with adjuvant arthritis compared to normal rats. The maximum vasopressor response to noradrenaline, E_{Am}, was successively reduced in the inflamed leg from days 0-3 to days 14-16 after injection of FCA into the paw.

Simultaneous injection of 6-OHDA (60μg /per paw) with FCA resulted in increased paw swelling in the primary phase of arthritis, E_{Am} to noradrenaline was further depressed. A slight increase in the pD_2 value of noradrenaline was seen in inflammation, but this increase seems to be of no theoretical and practical significance.

Injection of 6-OHDA (60μg) into the paw of normal non-arthritic rats likewise resulted in a decrease of E_{Am} and an increase of pD_2 of noradrenaline in the isolated perfused hind legs up to day 5 after 6-OHDA injection. Then, E_{Am} slightly increased, but pD_2 decreased until day 12 after the 6-OHDA injection. It would be interesting whether E_{Am} will further increase due to sensitization by 6-OHDA evoked chemical denervation at later times after 6-OHDA injection. In rats injected with 6-OHDA into the same paw 5 days before FCA injection, E_{Am} increased in the isolated perfused hind leg from day 3 to day 5 of arthritis. No explanation can be given for this effect.

CONCLUSIONS

Here, we report that the injection of 6-OHDA increases paw swelling in a time-dependent manner and that adjuvant arthritis changed the vasoreactivity compared to normal non-arthritic rats (control).

Conflict of interest

The author declares that they have no conflict of interest.

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