Blood and plasma viscosity after experimental ischaemia in healthy normolipidaemic volunteers treated with suloctidil

	Blood viscosity Pre-ischaemic	Post-ischaemic	Plasma viscosity Pre-ischaemic	Post-ischaemic
Group 1				
Control	2.51 ± 0.12	3.34 ± 0.32*	1.30 ± 0.10	1.37 ± 0.13
Suloctidil[a]	2.58 ± 0.12	2.70 ± 0.15**	1.34 ± 0.18	1.33 ± 0.14
Group 2				
Control	2.65 ± 0.20	3.41 ± 0.22*	1.32 ± 0.15	1.35 ± 0.08
Suloctidil[b]	2.61 ± 0.22	2.63 ± 0.15**	1.36 ± 0.12	1.33 ± 0.13

Values are expressed in centipoise (mean ± SE). [a] 4 × 100 mg 1 day before the trial. [b] 300 mg immediately before the trial. * $p < 0.01$ versus the pre-ischaemic control values. ** $p < 0.01$ versus the post-ischaemic control values.

blood viscosity of the volunteers was measured in pre- and post-ischaemic samples 1 day before the treatment with Suloctidil (control values). The drug was given orally in 4 doses of 100 mg within 24 h (6-h intervals) to a group of 6 volunteers (3 males and 3 females, group 1), and in a single dose of 300 mg to the other 6 subjects (3 males and 3 females, group 2). A 2nd ischaemic trial was induced 2 h after the last administration of the drug, and the viscosity of plasma and blood was again measured with a Coulter Harkness Viscosimeter. Statistical differences were calculated using the Student's t-test.

Results and discussion. The occlusion of an arm, until ischaemic pain occurred, resulted in an increase in blood viscosity in all volunteers, while plasma viscosity was not influenced by the ischaemic episode (table). A very significant reduction of blood viscosity was observed in subjects treated with Suloctidil 1 day before (group 1) or immediately before (group 2) the ischaemic trial. Suloctidil treatment did not result in any change of plasma viscosity, neither before nor after the ischaemic trial.

It has been reported that the non-Newtonian behaviour of blood largely depends on the deformability of erythrocytes and their aggregation capability[9]. Since experimental ischaemia failed to increase plasma viscosity, the blood red cells appeared to be the major factor responsible for the increased post-ischaemic blood viscosity. Thus, the mechanism of action of Suloctidil, as a drug lowering the post-ischaemic blood hyperviscosity seems, at least partially, to involve the erythrocytes. Accordingly, it is possible to speculate that the drug may preserve the erythrocytes' deformability during an ischaemic episode.

In conclusion, the lowering effect of Suloctidil on blood hyperviscosity, together with its platelets antiaggregating[10] and spasmolytic[11] activity, could help to explain the therapeutic action of the drug in patients with vascular insufficiency.

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Possible 5-hydroxytryptamine component in the effect of apomorphine in isolated cerebral and peripheral arteries

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Summary. The effect of apomorphine was studied in isolated perfused rabbit arteries contracted by high potassium concentrations. The influence of methysergide suggests that apomorphine responses in central ear arteries, but not in middle cerebral arteries, are partially mediated by serotonin receptors.

Several studies have demonstrated that dopaminergic agonists are able both to contract and dilate cerebral and peripheral vessels[1]. Using adrenergic antagonists, it has been shown that alpha-adrenergic receptors participate in the dopamine contraction[2]. Moreover, hypotheses have been advanced by authors working on cerebral arteries[3] or peripheral arteries[4] according to which dopamine may have a 5-hydroxytryptamine (5-HT) contractile component. However, the results obtained using dopaminergic relaxation to demonstrate this possibility need further study.

The above findings led us to investigate in vitro the influence of methysergide, a 5-HT antagonist, on the vasoactive effect of apomorphine, a dopaminergic agonist, in middle cerebral and central ear arteries from rabbits.

Material and methods. Segments of middle cerebral (8 mm long) and of central ear (10 mm long) arteries were obtained from adult male rabbits (Fauve de Bourgogne). They were isolated for cannulation and perfused with a modified Tyrode medium maintained at 37 °C and at pH 7.30–7.45 and continuously aerated by an O_2 (95%) - CO_2

EC_{50}-values and maximum relaxations (E_{Am}) calculated from concentration-response curves plotted for apomorphine in middle cerebral and central ear arteries from rabbits

Pretreatment	Middle cerebral arteries			Central ear arteries		
	n	EC_{50} (moles · l^{-1})	E_{Am} (%)*	n	EC_{50} (moles · l^{-1})	E_{Am} (%)*
Control	7	$(3.6\pm1.1)\times10^{-7}$	58 ± 8	7	Contraction	
Methysergide 2.8×10^{-6} moles · l^{-1}	7	$(1.7\pm0.7)\times10^{-6}$	70 ± 7	6	$(3.4\pm0.6)\times10^{-5}$	91 ± 3
Phenoxybenzamine 3×10^{-5} moles · l^{-1}	12	$(2.3\pm0.9)\times10^{-7}$ [a]	84 ± 6 [b]	6	$(3.5\pm1.0)\times10^{-6}$ [c]	69 ± 5 [d]
Methysergide 2.8×10^{-6} moles · l^{-1} + phenoxybenzamine 3×10^{-5} moles · l^{-1}	7	$(8.0\pm3.7)\times10^{-7}$	84 ± 5 [b]	6	$(1.4\pm0.5)\times10^{-5}$ [a]	94 ± 2 [e]

Results are expressed as mean ± SE. [a] $p<0.05$ (comparison with methysergide). [b] $p<0.05$ (comparison with control); [c] $p<0.001$ (comparison with methysergide); [d] $p<0.01$ (comparison with methysergide); [e] $p<0.001$ (comparison with phenoxybenzamine). * E_{Am} is expressed as percentage of the maximum papaverine (10^{-4} moles · l^{-1}) relaxation.

(5%) mixture. Flow rate was constant during each experiment. Perfusion pressure was monitored with a pressure transducer connected to a potentiometric recorder. All drugs were introduced into the perfusion reservoir. Paired arteries from the same animal were tested in the same organ bath. After equilibration for 40 min and treatment with high K^+ solution (30 mmoles · l^{-1} in middle cerebral arteries and 100 mmoles · l^{-1} in central ear arteries) to induce a steady contraction in order to reveal clear-cut dilatory responses, cumulative concentration-response curves were run with apomorphine (concentrations in the medium from 3×10^{-8} moles · l^{-1} to 10^{-4} moles · l^{-1}). Apomorphine doses were added before treatment (control curve) and after introduction of the drugs: phenoxybenzamine (3×10^{-5} moles · l^{-1}) methysergide (2.8×10^{-6} moles · l^{-1}) or phenoxybenzamine plus methysergide in the same concentrations as above. These concentrations were chosen according to the results of previous studies[3,5]. These drugs were applied to the vessels for 20 min and remained in the perfusion fluid while apomorphine was added. At the end of each experiment, papaverine was introduced into the perfusion fluid (10^{-4} moles · l^{-1}) as an arbitrary reference. The relaxant response of apomorphine was characterized by the median effective concentration (EC_{50}) and the maximum response (E_{Am}) established from the concentration-response curves. The E_{Am} was expressed as a percentage of the maximum relaxation induced by papaverine. Statistical comparisons were made using Student's t-test.

Results and discussion. After an active tone was given with K^+ solution, apomorphine induced a concentration-dependent relaxation in middle cerebral arteries but produced a slight contractile effect in central ear arteries. Methysergide did not influence the vasodilator action of apomorphine in middle cerebral arteries, either in the absence or in the presence of phenoxybenzamide. EC_{50} and E_{Am} were similar in each case (table). In central ear arteries, apomorphine induced a contractile response which was reversed to dilatation after treatment with phenoxybenzamine or methysergide. As shown in the table, the maximum relaxation due to apomorphine (E_{Am}) was higher with methysergide than with phenoxybenzamine, but its affinity was lower. Moreover the comparison of EC_{50} values indicated that apomorphine had a higher relaxant potency in middle cerebral arteries than in central ear arteries after pretreatment with methysergide, phenoxybenzamine or methysergide plus phenoxybenzamine.

Our results suggest that the relaxant effect of apomorphine in rabbit middle cerebral arteries does not implicate 5-HT receptors. On the contrary, the apomorphine response in central ear arteries seems to involve the activation of 5-HT receptors, given that methysergide, a competitive 5-HT receptor antagonist in peripheral arteries[5], was able to potentiate apomorphine relaxation.

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Effects of fluoride on glycosaminoglycan of cancellous and cortical bone of rabbits

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Summary. The present report deals with the effect of excessive ingestion of fluoride on glycosaminoglycan (GAG). Increase in fluoride deposition in bone, and in circulating levels of fluoride in serum, are also reported. Among the 3 constituents of GAG investigated; hexosamine, uronic acid and sulphate, the content remained unaltered except for sulphate.

It is reasonably well established that fluoride poisoning affects the structure and normal functioning of both osseous and non-osseous tissues[2-7]. The mineralization process in skeletal tissues has been reported to be defective in fluoride poisoning[8,9]. One of the possible explanations for defective mineralization in bone is that the organic matrix of bone might be abnormal. Indirect evidence obtained through autoradiographic (using S^{35}) and other histochemical studies suggest changes in glycosaminoglycans (GAG) in bone and tooth during mineralization[10-12].