time when the lung was not oedematous (table) and yet efflux of PQ was unaffected. It therefore appears that during the early stages of PQ toxicity the pulmonary uptake of PQ is selectively affected.

The lack of efflux of PQ form lung slices[6,7] indicates that the PQ molecule is unable easily to retraverse the cellular membrane once it is in the intracellular environment, owing either to tight tissue binding or to its being ionized intracellularly or requiring a transport process for removal that may have been destroyed upon entry. However, it has been suggested that the pulmonary uptake and retention of PQ may not be related to any binding process[16]. Both PQ and 5HT are accumulated by the lung via active, energy dependent processes[11-14]. Since 5HT uptake was unaffected, it is unlikely that the reduction in PQ uptake represents a general inhibition of energy producing processes. However, 5HT is accumulated by pulmonary endothelial cells[11,12] whereas it is speculated that PQ uptake occurs in type I and type II alveolar cells[14], as it is these cells which are first damaged in vivo by PQ. 16 h after 100 μmoles PQ kg^{-1}, i.v., rat lung contains 10–15 nmoles PQ/g tissue (unpublished observations). This is approximately 20–30% of the amount of PQ accumulated in vitro in 2 h by untreated lung slices, and 50–75% of that accumulated by lung slices from PQ-treated rats. Thus, by virtue of there being substantial amounts of PQ in the lung 16 h after in vivo administration, and since this is presumably localized in those cells possessing the necessary PQ transport mechanism, it is possible that PQ may selectively inhibit its own active transport. This could occur by selective cellular damage or competitive inhibition of ^{14}C-PQ uptake by the residual pool of unlabelled PQ in the lung. Unlike PQ and 5HT, IP is accumulated by mammalian lungs by diffusion and tissue binding[10]. When lung slices from untreated rats are incubated in the presence of both IP and PQ, more IP is accumulated than if the slices were incubated with IP alone (unpublished observations). Similarly, the active uptake of phenol red by lung slices is increased in the presence of paraquat[17] and the in vitro binding of chlorphentamine to rat lung 15,000 × g subcellular fraction is increased by PQ[18]. It was, therefore, surprising that in vivo PQ pretreatment did not alter pulmonary IP accumulation.

The results presented in this communication suggest that the failure of drugs[6-8], possessing the potential of displacing PQ from the lung, to ameliorate PQ-induced pneumotoxicity is unlikely to be due to altered pulmonary uptake of the displacing drug.

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Effect of suloctidil on blood viscosity in healthy volunteers after forearm occlusion

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Summary. The effect of suloctidil (1-(4-isopropylthiophenyl)-2-n-octylaminopropanol) on increased blood viscosity was studied in healthy volunteers after forearm occlusion. A significant reduction of blood viscosity was observed in subjects treated 1 day before, or immediately before, the ischaemic trial. It is concluded that the drug may preserve the deformability of erythrocytes during an ischaemic episode.

Vascular diseases of the legs are, in many cases, accompanied by abnormally high blood viscosity[1,2]. In patients with claudicatio intermittens, hyperviscosity appears to carry a worse prognosis[1]. The high blood viscosity is commonly associated with an increased tendency of the red cells to aggregate and with an increase in total fibrinogen levels. The ability of the erythrocytes to change form seems to be impaired[3], as well.

In the present study we have verified that ischaemic obstruction of the forearm leads to an increase of blood viscosity in healthy normolipidaemic volunteers. Moreover, we studied under these conditions the effect of suloctidil (1-(4-isopropylthiophenyl)-2-n-octylaminopropanol), a new drug found to be able to reduce blood hyperviscosity[4-6], used also for the treatment of claudicatio intermittens[7].

Materials and methods. The study was performed on 12 healthy normolipidaemic volunteers (6 males and 6 females, 18–32 years old). Selection criteria were a minimal 2-month drug-free period before the present study, and no smoking habit. Experimental ischaemia was induced as described previously by De Clerck et al.[8] by occlusion of the upper arm with a blood pressure cuff at a pressure above 200 mm Hg, followed immediately by compressing a rubber bulb in the hand at a standard rhythm, until ischaemic pain precluded further exercise. Plasma and

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