augmented entry of the amino acid is the result of an increased transport rather than metabolism since a similar increase in the uptake of the metabolizable amino acid isoleucine as of the nonmetabolizable analogue cycloleucine was observed in the isolated microvessels. The complete inhibition of the increased isoleucine uptake by the cold cycloleucine supports this contention and indicates the involvement of the carrier mediated process. Hence, the increased uptake of phenylalanine could also be due to the specific passage and not metabolism. It is of interest that such a change was not seen in the capillary uptake of glutamine which belongs to the substances characteristic for low level passage across the BBB[5-7]. However, a similar increase in the specific uptake of these amino acids was seen in the cerebral capillaries exposed to a medium containing NaCl under anaerobic conditions only (unpublished observations). Therefore, it is possible that the ischemic and postischemic increased capillary uptake of the labeled isoleucine, cycloleucine and phenylalanine may be due to ionic changes and altered reactivity of the carrier mediated process for these substances.

In conclusion, selective and diverse effects of cerebral ischemia and postischemia on the capillary uptake of the neutral amino acids and on the previously reported entry of ^{3}H 2-DG[3,4] could be responsible for the different passage of these substances across the BBB under these conditions.

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Nerve-growth promoting action of isaxonine in rat

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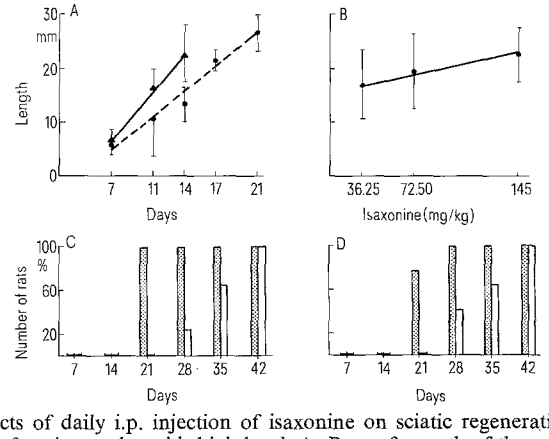
Summary. After sciatic nerve lesion by freezing, the length of the most rapidly regenerating fibres was significantly increased by i.p. injection of isaxonine (N-isopropyl-amino-2-pyrimidine orthophosphate) in the rat. A dose-effect relationship was demonstrated. Both sensory and motor function returned earlier in treated animals.

After nerve injury, the process of nerve regeneration is slow. It may be possible that drugs which accelerate nerve growth could be useful in the clinical treatment of nerve injuries, as well as a tool for investigating mechanisms controlling nerve growth and regeneration. We reported recently[1] that isaxonine[2] (N-isopropyl-amino-2-pyrimidine orthophosphate), a newly synthesized drug, promotes a powerful neurite outgrowth in the cultured spinal ganglion of the mouse. The present experiments examine the possible nerve growth promoting action of isaxonine in vivo in rat.

We compared the rate of regeneration of the sciatic nerve in control animals (Wistar males 180±5 g) with that of animals receiving isaxonine. The sciatic nerve was frozen at the mid-thigh level with a thermode 2 mm in diameter, maintained at −20 °C for 20 min[3]. This technique produces standard axon damage and wallerian degeneration. It does not disrupt the nerve sheath, leading to a more homogeneous rate of axon growth[4,5]. The length of regenerated fibres was measured electrophysiologically in a nerve chamber[6]. The sciatic nerve was excised under nembutal anaesthesia and immersed in paraffin oil at 37.5 °C in the chamber containing a grid of platinum electrodes 1 mm apart. The extremity of the most rapidly growing fibres was determined by measuring the distance between nerve injury and the most distal pair of electrodes from which an action potential could be detected after 12 summations. A computer-assisted technique made possible the sequential recording from 12 pairs of electrodes surrounding the extremity of regenerating fibres within 90 sec: this delay is shorter than the time required for alteration of action potential in the regenerating nerve after excision[3].

Measurements were carried out on groups of 10 animals 7, 11, 14, 17 and 21 days after the lesion (figure A). One series of treated animals received 145 mg of isaxonine (LD 50/10) i.p. each day. The rate of regeneration calculated from the slope of the regression line was 1.6 (±1.28 SE) mm/day in the control group and 2.3 (±1.17 SE) mm/day in isaxonine treated animals (+44%). Covariance analysis using the



Effects of daily i.p. injection of isaxonine on sciatic regeneration after freezing at the mid-thigh level. A: Rate of growth of the most rapidly regenerating axons as demonstrated by recording of action potential in a nerve chamber. Experimental points show the mean ±SD of the length from the lesion to the most distal electrode from which action potential could be recorded as a function of the postoperative day. The mean recovery rate is calculated by taking the reciprocal of the slope of the regression line. Dottet line = controls; solid line = animals treated with isaxonine 145 mg/kg daily (LD 50/10). B: Dose-effect regression line: length ±SD of the most rapidly regenerating axons 14 days after the lesion as a function of drug concentration. C and D: Effects of isaxonine (145 mg/kg daily) on the return of sensory (C) and motor (D) functions; striped bars = isaxonine-treated animals; white bars = controls injected with saline.

F-test[7] showed that the slopes of the 2 regression lines were significantly different ($p < 0.05$).

A dose-effect relationship was sought by comparing the effects of 3 doses of isaxonine administered over 14 days after the lesion, as shown in the figure, B. Covariance analysis demonstrated that the slope of the dose-effect regression line was significantly different from a line parallel to the abscissa ($p < 0.01$).

Recovery of sensory and motor functions in rats was investigated on groups of 20 animals tested independently by 2 observers. Sensory recovery was appreciated by the reappearence of a behavioural response to electrical stimulation of the plantar surface of the digits on the lesioned side (2 shocks of 1 msec, interval 1 msec, 180 V). The motor response was tested by searching for the reapparance in the lesioned leg of a gripping reaction obtained by drawing the 4 legs backward on the table[8]. The figure, C and D, shows that recovery of sensory and motor responses had occurred in all animals of the control group by day 42. In the treated group, recovery of the sensory and motor responses were observed in all animals by days 21 and 28, respectively.

Results confirm in vivo the positive effect of isaxonine on nerve elongation, observed previously in vitro. They show significant enhancement of the rate of sciatic fibres regeneration associated with consistent increase in rate of sensory and motor recovery.

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Plasma lipid concentration and lipoprotein distribution in exercising and nonexercising rats fed a high sucrose diet

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Summary. Voluntary physical activity in rats fed a high sucrose diet reduces the plasma triglyceride level but has no major influence on the lipoprotein distribution.

There are several studies on the effect of physical activity on plasma lipid concentration[2-9], while little information seems to be available on the effect of physical activity on plasma lipoprotein distribution. In a group of very active men, Wood et al.[10] observed that the level of high density lipoprotein cholesterol was higher and the level of low density lipoprotein cholesterol lower than in a control group of relatively inactive men. These findings are significant in light of epidemiological studies suggesting that the level of high density lipoproteins is associated with reduced risk and the level of low density lipoproteins with enhanced risk of developing coronary heart disease[11-17]. More direct evidence for a causal effect of physical activity on the plasma lipoproteins was obtained by Lopez-S et al.[18], who showed that α-lipoproteins increased and β-lipoproteins decreased in men following 7 weeks of severe exercise.

We recently reported that the level of voluntary physical activity in rats is an inheritable phenomenon[19]. Surprisingly, in genetically active rats there was a pronounced age-related increase in the plasma cholesterol and triglyceride concentration; while no such increase was observed in genetically passive rats. However, nonexercising subgroups of both types of rats had a similar plasma lipid level as the corresponding exercising group. The rats were fed a stock diet and the lipoprotein distribution was not investigated.

We recently observed that a high sucrose diet increased the plasma lipid level and appreciably affected the lipoprotein distribution[20]. In the present study we have investigated whether physical activity might influence plasma lipid concentration and the lipoprotein distribution in genetically active rats fed this high sucrose diet.

Material and methods. Genetically active female Wistar rats

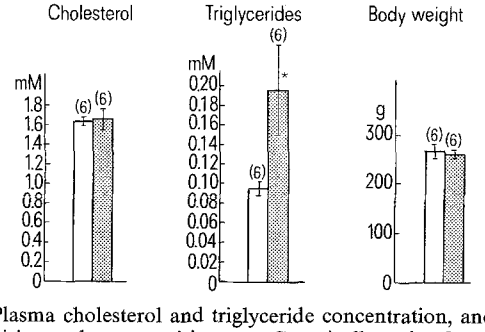

Fig. 1. Plasma cholesterol and triglyceride concentration, and b.wt of exercising and nonexercising rats. Genetically active female rats were divided into exercising (open columns) and nonexercising (striped columns) subgroups as described in text. Both groups were fed the same purified high sucrose diet for 3 months. Mean values ±SEM are shown with number of rats in each group. *$p < 0.05$ vs exercising rats (Wilcoxon's test for 2 samples[21]).

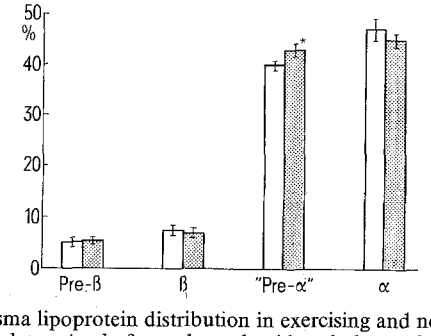

Fig. 2. Plasma lipoprotein distribution in exercising and nonexercising rats as determined after polyacrylamide gel-electrophoresis and densitometric scanning. Lipoprotein distribution is presented as percent of total weight of the transferred densitogram. Total weight of densitogram was 0.401±0.021 g and 0.394±0.026 g for the exercising and nonexercising group, respectively. Symbols are as in figure 1. *$p < 0.05$ vs exercising rats.