and citrate cleavage enzyme by 43 and 39% respectively. Lactate dehydrogenase exhibits an activity that is increased by 48 and 30% respectively; in the case of malic enzyme the increase of activity lies by 294 and 147% respectively, and therefore is more pronounced. On the other hand, citrate synthase rises by only 12 and 9% respectively.

In animal experiments the optical antipodes of the compound CH 13437 cause the same alterations in enzyme activities. Neither qualitatively nor quantitatively do they differ in their influence upon liver metabolism. The relative liver weight increases by 4.2% and 7.2% respectively, as compared to the control group (Table II).

In accord with the assumption that the hypolipidaemic action of the drug may be found in a direct influence upon the liver metabolism[1,2], the decrease of triglyceride, measured by the drop in total glycerol, is virtually equal for the antipodes, i.e. 34% for (—)-CH 13437 and 36% for (+)-CH 13437 (Table II).

The increase in free fatty acids in the serum may be connected with inhibition of 3′, 5′-AMP-phosphodiesterase; inhibition of this enzymatic step leads by way of an increase of the 3′, 5′-AMP level to a lipase activation and thus to increased lipolysis[16]. In vitro, 3′, 5′-AMP-phosphodiesterase is inhibited by CH 13437 to approximately the same degree as by theophyllin[17].

The changes in liver enzyme activities, especially reduction of the citrate cleavage enzyme, which are observed after several days of treatment with the drug, lead to inhibition of lipogenesis as the cause of the hypolypidaemic action[6]. In the rat an increase of the smooth, endoplasmatic reticulum of the liver cell, which is also morphologically detectable, and an elevation of the activities of constitutive enzymes are probably the activating primary factors. This results in an induction of NADPH-cytochrome c-reductase and other microsomal enzymes[18]. The increased influx of reduction equivalents via NADPH oxidation induces the malic enzyme. The greater demand for reduction equivalents is initially made available as NADH, as the lactate dehydrogenase activity is increased and makes possible an accelerated dehydrogenation of the lactate transported to the liver. Via an ATP-dependent reaction cycle which proceeds between pyruvate, oxaloacetate and malate, hydrogen may be transferred from NADH to NADPH. Its oxidation finally can be achieved by the microsomal NADPH-cytochrome c-reductase. The increased consumption of ATP is thought to be covered by a greater degradation of fat; the rise in free fatty acids in the serum and the increase of citrate synthase activity in the liver are an indication for this concept. By way of still unknown feedback mechanisms, a supression of the citrate cleavage enzyme occurs and, consequently, reduced lipogenesis results. The decrease in activity of the glycolytic key enzymes, fructose-6-phosphate kinase und pyruvate kinase, leads to a delay of glucose degradation in the liver; the reduced acetyl-CoA requirement which may be attributed to the inhibition of lipogenesis, is reflected in this.

The studies show that both antipodes of compound CH 13437 have a similar influence on the liver metabolism and consequently have an equally strong hypolipidaemic effect which is in direct correspondence with the one shown be the racemate.

*Zusammenfassung.* Die optischen Antipoden der hypolipidämisch wirkenden Substanz 2-Methyl-2-[*p*-(1, 2, 3, 4-tetrahydro-1-naphthyl)-phenoxy]-propionsäure (CH 13437) zeigen im Rattenversuch gleichstarke hypolipidämische Wirkung und gleichartige Aktivitätsänderungen von Leberenzymen des Kohlenhydrat- und Lipidstoffwechsels.

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## Sympathetic Influence on Cerebral Blood Volume: Time-Dependent Effect of Decentralization of the Superior Cervical Ganglia in Mice

Although the pial arterial system receives a very extensive sympathetic innervation[1–5], the significance of the neural influence on brain circulation is highly controversial. One reason is that the results even of basic experiments, such as postganglionic denervation, appear conflicting because little attention is usually paid to the length of time that has elapsed after the operation. It has recently been shown[6] that the cerebral blood volume (CBV) of mice varies markedly depending on the time following bilateral excision of superior cervical sympathetic ganglia. Shortly after operation there is a leakage of the noradrenaline transmitter from the degenerating nerve terminals with an accompanying activation of the vascular receptor (the CBV was found to be reduced by 28%). When the transmitter has disappeared from the degenerating terminals, the neural influence on the vessels is abolished (the blood volume was increased by 34% compared to unoperated controls). About 2 weeks later, a pronounced denervation supersensitivity of the vascular receptors to circulating catecholamines develops (the CBV became normal or even subnormal).

Another circumstance giving the impression of inconsistent results after denervation is that a difference in the effects of pre- and postganglionic operation is usually not fully considered. The present report shows that the time-dependent changes in CBV are significantly different when

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decentralisation (preganglionic denervation) of the superior cervical sympathetic ganglia has been performed as compared with ganglionectomy (postganglionic denervation).

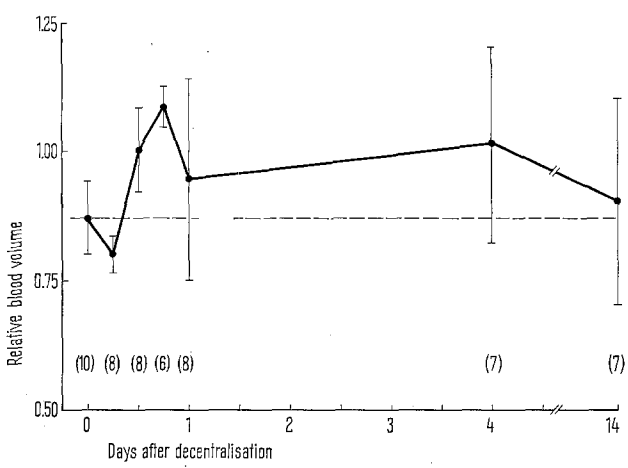
*Material and methods.* The material comprises 72 male albino mice (about 25 g body weight), maintained on standard pellet food (SAN-bolagen, Sweden) and tap water ad lib. Decentralisation of the superior cervical ganglia (44 animals) was performed by bilateral sectioning of the sympathetic trunk 3 mm below the ganglion under light ether anesthesia. The CBV was determined 6, 12, 18, 24 h and 4 and 14 days later. Sham-operation was made in 18 animals and the blood volume was measured after 6 h (9 animals) and 18 h (9 animals). 10 animals served as unoperated controls.

A solution of human serum albumin (0.3–0.5 mg/ml of physiological saline) labelled with radioactive iodine ($^{131}$I, 50 μCi/ml; RISA, AB Atomenergi, Sweden) was injected into the tail vein of the unanesthetized animal (0.2 ml per animal of the solution diluted with saline to a calculated final activity of 2.5 μCi). 6 min was allowed for mixing, after which the animal was killed by rapid immersion into liquid nitrogen. The brain and 5 cm of the proximal small intestine (used as reference tissue) were dissected out, weighed, and radioactivity was read without previous homogenization in an autogamma spectrometer (Packard). The selection of reference tissue and the precision of the technique have previously been discussed[6]. The result expressing the relative CBV for each animal was expressed as the ratio of cpm/g brain tissue to cpm/g intestinal tissue.

*Results and comments.* The variations in CBV at various time-periods after superior cervical ganglionectomy[6] are consistent with the view that the sympathetic nerves to the intracranial vessels are vasoconstrictory. The time-dependent effect of decentralisation on the relative CBV is demonstrated in the Figure. The general pattern of changes in CBV during the first post-operative 24 h is similar whether denervation has been postganglionic[6] or preganglionic (Figure), except that the peak decrease and increase in CBV occur 6 h earlier in the decentralised animals. It is conceivable that the changes during the first 24h are associated with degeneration of the severed nerves[6]. Thus, initially after sectioning the preganglionic (cholinergic) nerve fibres there is a transient activation of the effector structure[7,8] (i.e. the superior cervical ganglion) probably as a consequence of transmitter leakage[9,10] from the degenerating nerve terminals, and the CBV therefore shows a tendency to reduction at 6 h (Figure). Subsequently, when the transmitter has disappeared from the preganglionic nerve terminals, the activation subsides and the synaptic transmission becomes impaired and is then abolished[9–11]. This would agree with a dilatation of the sympathetically innervated brain vessels and hence with the highly significant (Student's $t$-test: $p < 0.01$) increase in CBV compared with the unoperated controls at 18 h. There was no significant difference in CBV when comparing the sham-operated and unoperated animals. The above-mentioned earlier appearence of CBV changes in the decentralised animals can be explained by an earlier manifestation of the degenerative phenomena in the nerve terminals since they occur at a shorter distance from the point of injury than in the ganglionectomized animals.

At 4 and 14 days after postganglionic denervation the previously innervated receptors attain a considerable degree of supersentitivity to circulating catecholamines[12] and, in the case of the brain vessels, the tone increases, which is accompanied by a normal or even subnormal CBV[6]. On the other hand, the degree of supersensitivity after decentralisation is known to be less pronounced[12]. This is in accordance with the findings (Figure) that the mean CBV in the decentralised animals is constantly above the level of the controls at 4 and 14 days after the operation reflecting a sustained pial vasodilation.

The present findings have offered further evidence in favour of the assumption a) that the sympathetic nervous system exerts a vasoconstrictor influence on cerebral vessels; b) that the sympathetic nerves to these vessels originate in superior cervical ganglia; c) that the circulatory changes after interference with the cranial sympathetic nerves are highly time-dependent, and d) that the effect of preganglionic denervation of the brain vessels is different from that of postganglionic denervation.




Relative cerebral blood volume (ratio of plasma volume of the brain to plasma volume of the reference tissue – small intestine – calculated from cpm per gram brain/cpm per gram intestinal tissue after i.v. injection of $^{131}$I-labelled albumin) before and after different periods of decentralization (preganglionic denervation) of the superior cervical sympathetic ganglia. Mean ± S.E.M. Dashed line indicates control level of cerebral blood volume obtained in the unoperated animals. Number of animals within parenthesis.

*Zusammenfassung.* Neue Befunde über die Neuronale Regulation der Hirndurchblutung. Durchschneidung der präganglionären Fasern des Hals-Sy. verursachen eine starke Initiale und eine etwas weniger ausgeprägte Dauerzunahme der Durchblutung, was durch Unterbrechung der Innervation und Sensitivierung der Rezeptoren erklärt wird.

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