Modification of the cerebrovascular response to noradrenaline by bile duct ligation

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SUMMARY The effects of intracarotid infusions of noradrenaline on the cerebral vasculature were studied in seven baboons with bile duct ligation. Infusion of 8 μ g and 16 μ g/min of noradrenaline resulted in a significant decrease in cerebral blood flow in the jaundiced animals. In normal baboons, these doses produced cerebrovascular dilatation. These results indicate that there is an increased cerebrovascular sensitivity to noradrenaline in the obstructive jaundice which follows bile duct ligation. It is postulated that noradrenaline smooth muscle uptake mechanisms are disturbed allowing a greater concentration of the amine at the receptor sites.

Recent studies in the baboon have indicated that there is an increased renovascular sensitivity to noradrenaline with bile duct ligation (Bloom, Bomzon, Rosendorff, and Scriven, 1974). Similarly, experiments on an isolated artery preparation have shown potentiation of the pressor effects of noradrenaline by plasma obtained from these baboons (Bloom, McCalden, and Rosendorff, 1975a). These results suggest that there is a heightened pressor response to circulating catecholamines in the obstructive jaundice following bile duct ligation.

The present study was evolved to examine the possibility that a similar hypersensitivity to noradrenaline exists in the cerebral vascular bed in baboons with duct ligation. This may elucidate some of the unexplained symptoms of cerebral dysfunction in hepatic disease (Sherlock, 1968).

Materials and Methods

Studies were carried out on 16 adult baboons (*Papio ursinus*) weighing 9-16 kg. In seven of the animals an obstructive jaundice was produced by surgical ligation of the common bile duct two weeks before the experiments on cerebral blood flow. All the animals were sedated with 0.2 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis) administered by intramuscular injection, and full anaesthesia was induced with intravenous injection of 20-30

mg/kg pentobarbitone sodium (Nembutal, Abbott). The animals were then intubated and anaesthesia was maintained with a 3:2 mixture of oxygen and nitrous oxide with similar quantities of barbiturate given to each group as required. A catheter was introduced into the femoral artery to measure intraarterial blood pressure via an electromanometer (Statham P23AA) and to enable arterial blood sampling for determinations of PaCO₂, PaO₂ and pH on an Instrumentation Laboratories' blood gas analyser (IL 313). The right carotid bifurcation was exposed and a fine catheter was inserted into the lingual artery until its tip just entered the external carotid artery. The external carotid artery and all its remaining branches were then ligated. Cerebral blood flows were measured by an intracarotid ¹³³xenon washout technique. A bolus of 30 μ Ci of ¹³³xenon in 0.2 ml of saline was injected into the lingual catheter and was washed retrograde down the external carotid artery into the internal carotid. The cerebral uptake and clearance of ¹³³Xe was monitored using a 5-cm diameter sodium iodide detector mounted posteriorly over the parietal region. A high degree of collimation was used to exclude the possible radiation arising from non-cerebral orbital tissues. This was confirmed by the absence of a third flow component (extracranial perfusion) in the clearance curves. After the initial peak of activity the clearance data were recorded for at least 15 min in digital form with a Nuclear Enterprises' data logging system. When exceptionally slow flows were found this record was extended to 20 minutes. The washout curves were

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analysed manually and by computer (using a least squares fitting programme) into two exponential components representing flow through cerebral grey and white matter respectively.

When surgery was completed the bladder was catheterized and allowed to drain freely. The animals were paralysed with 10 mg/kg of intravenous Scoline (Glaxo-Allenburys) and were ventilated using a Harvard variable phase respirator. This, together with the EEG, pulsatile and mean arterial blood pressure, central venous blood pressure and the analogue xenon washout curve were recorded on a Beckman dynograph recorder. The EEG was used to standardize the depth of anaesthesia. Measurements of cerebral blood flow were only made when the EEG was stable and showed a frequency of 9 to 12 Hz. Throughout the experiment the arterial PaCO_2 and PaO_2 were kept approximately 35 and 100 mm Hg respectively and body temperature was kept at 37°C by radiant heating. After a stabilization period of approximately one hour, two control cerebral flow measurements were made. Noradrenaline was then infused via the lingual artery at $8\text{ }\mu\text{g/min}$ and after 10 minutes the flow again determined. The noradrenaline was then stopped and after a further 10 minutes another control measurement was made. Using this protocol the cerebrovascular response to $8\text{ }\mu\text{g/min}$, $16\text{ }\mu\text{g/min}$ and $32\text{ }\mu\text{g/min}$ of noradrenaline was determined. All doses of noradrenaline refer to the salt.

In addition arterial blood samples were taken for serum urea, sodium, potassium, chloride, bilirubin (direct and indirect), alkaline phosphatase and renin measurements. An attempt was made to correlate the degree of cerebrovascular constriction in response to the noradrenaline with the alteration in these serum constituents after bile duct ligation

Results

The mean grey matter blood flow was the variable

used in this study since measurement of white matter flow is less accurate (Lassen, 1974). The mean cerebral blood flow in the control animals was 57.3 ml/min/100 g tissue and this increased to 65.8 and 64.1 ml/min/100 g tissue when noradrenaline was infused at $8\text{ }\mu\text{g/min}$ and $16\text{ }\mu\text{g/min}$ respectively. A fall in cerebral blood flow to 53.4 ml/min/100 g tissue was observed with $32\text{ }\mu\text{g/min}$ of noradrenaline (table I). The increase in flow recorded with $8\text{ }\mu\text{g/min}$ was significantly different from the baseline ($P < 0.05$) whereas no significant difference was found with $16\text{ }\mu\text{g/min}$ and $32\text{ }\mu\text{g/min}$. In the jaundiced animals the mean baseline grey matter flow was 59.1 ml/min/100 g tissue and with infusion of noradrenaline the mean values fell to 49.9 , 48.8 and 52.2 ml/min/100 g tissue with $8\text{ }\mu\text{g/min}$, $16\text{ }\mu\text{g/min}$ and $32\text{ }\mu\text{g/min}$ infusion rates respectively. The changes in flow were significantly different from the control values at the $8\text{ }\mu\text{g}$ ($P < 0.005$) and $16\text{ }\mu\text{g}$ ($P < 0.25$) infusion rates but not at the $32\text{ }\mu\text{g}$ rate (table I). Throughout these experiments baseline measurements were made between the various doses of noradrenaline. There was no significant change in these baseline values as the experiments progressed.

The mean changes in cerebral blood flow when noradrenaline was infused with control animals and in jaundiced animals are shown in figure 1. In the control animals the infusion of noradrenaline at $8\text{ }\mu\text{g/min}$ and $16\text{ }\mu\text{g/min}$ produced a mean increase in cerebral blood flow of 8.4 ± 4.3 and $8.6 \pm 6\text{ ml}$ respectively, while at $32\text{ }\mu\text{g/min}$ this was reversed to a mean decrease of $1.7 \pm 4.9\text{ ml/min}$. In the jaundiced animals $8\text{ }\mu\text{g/min}$ and $16\text{ }\mu\text{g/min}$ produced a reduction of 9.48 ± 2.6 and $10.9 \pm 4.4\text{ ml/min}$ respectively. With $32\text{ }\mu\text{g/min}$ falls of 5.16 ± 3.6 were recorded. There was a significant difference between the controls and the jaundiced animals at the $8\text{ }\mu\text{g/min}$ ($P < 0.005$) and the $16\text{ }\mu\text{g/min}$ ($P < 0.02$) but not at the $32\text{ }\mu\text{g/min}$ infusion. The infusion of noradrenaline was associated with an increased

Noradrenaline ($\mu\text{g/min}$)	Cerebral Blood Flow (ml/min/100 g)	Mean Change in Cerebral Blood Flow (ml/min/100 g)	Mean Arterial Blood Pressure (mm Hg)	PCO_2 (mm Hg)
Normal				
0	57.3 ± 2.7	—	108.3 ± 7.7	36.7 ± 1.0
8	65.8 ± 5.2	8.41 ± 4.3	112.3 ± 7.2	34.6 ± 0.6
16	64.05 ± 6.5	8.60 ± 6.0	117.8 ± 8.8	34.7 ± 0.8
32	54.1 ± 12.2	-1.67 ± 4.9	126.7 ± 9.5	35.0 ± 0.3
Jaundiced				
0	59.09 ± 5.3	—	110.1 ± 6.2	34.7 ± 0.9
8	49.9 ± 4.1	-9.48 ± 2.6	120.7 ± 6.7	35.2 ± 0.8
16	48.8 ± 5.5	-10.9 ± 4.4	116.8 ± 4.6	35.5 ± 0.8
32	52.2 ± 5.7	5.16 ± 3.6	127.1 ± 3.6	34.9 ± 0.4

Table I Mean grey matter cerebral blood flow, mean change in cerebral blood flow, and mean arterial blood pressure in nine normal animals and seven jaundiced animals following infusions of noradrenaline¹

¹All values are shown ± 1 standard error of the mean.

Fig 1 Change in grey matter cerebral blood flow with noradrenaline. The mean change in grey matter cerebral blood flow (ml/min/100g tissue) during intracarotid infusion of noradrenaline (at 8 µg/min, 16 µg/min and 32 µg/min) in normal animals (closed circles) and in animals with obstructive jaundice (open circles). The vertical lines represent plus or minus 1 standard error of the mean and the P value is calculated between the normal and the jaundiced groups at the same dose of noradrenaline.

systemic blood pressure, and in order to take these increments into account, we have calculated the

cerebrovascular resistance $\left(\frac{\text{Pressure}}{\text{flow}}\right)$ (mm Hg/ml.

min⁻¹). The changes in cerebrovascular resistance are shown in figure 2. In the control animals 8 µg/min produced a decrease of 0.21 ± 0.12 mm Hg/ml.min⁻¹ while 16 µg and 32 µg/min produced an increase of 0.001 ± 0.11 and 0.425 ± 0.17 mm Hg/ml.min⁻¹ respectively. In the jaundiced animals all doses of noradrenaline produced an increase in cerebrovascular resistance coinciding with the decrease in cerebral blood flow. These changes in resistance were 0.66 ± 0.28 , 0.90 ± 5.56 and 0.71 ± 0.28 mm Hg/ml.min⁻¹ at 8 µg, 16 µg and 32 µg

Fig 2 Change in grey matter cerebrovascular resistance with noradrenaline. The mean changes in cerebrovascular resistance (mm Hg/ml.min⁻¹) during intracarotid infusion of noradrenaline (8 µg/min, 16 µg/min and 32 µg/min) in normal animals (closed circles) and jaundiced animals (open circles). The vertical lines represent plus or minus 1 standard error of the mean and the P value is calculated between the normal and the jaundiced groups at the same dose of noradrenaline.

infusion rates respectively. The responses were significantly different from the control animals at the 8 µg and the 16 µg levels ($P < 0.01$ and $P < 0.1$) respectively.

The arterial blood pH, PCO₂ and PO₂ were not significantly changed throughout the experiments. The range of pH was from 7.41 to 7.43 and the PO₂ from 98 to 130 mm Hg. The values for PCO₂ are shown plus and minus 1 standard error of the mean in table I. Increments in systemic arterial blood pressure were recorded during perfusion of noradrenaline. The increase was, however, similar in both groups of animals and the mean blood pressure ranged from 100 to 126 mm Hg which is well within the cerebral autoregulatory limits for the baboon (Strandgaard, MacKenzie, Sengupta, Rowan, Lassen, and Harper, 1974). The changes in pH, PCO₂ and PO₂ were minor, and would not be expected to alter significantly cerebral blood flow.

The mean values for bilirubin and other serum variables measured are shown in table II plus and minus 1 standard error of the means. There was no good correlation between the size of the cere-

Bilirubin			SGOT (Units)	SGPT (Units)	Alkaline Phosphatase (Units)	Na+ (m-equiv/l)	K+ (m-equiv/l)	Urea (mg %)	Plasma Renin (pg/ml/hr)
	Direct	Indirect							
Before	0.5	0.2	40 ± 3	44 ± 3	17.5 ± 3.3	141.0 ± 0.8	3.9 ± 0.2	43 ± 4	524 ± 92
After	13.6 ± 2.0	8.4 ± 1.2	67 ± 7	88 ± 19	360 ± 88.4	142.0 ± 1.3	4.0 ± 0.1	48 ± 4	548 ± 92

Table II Biochemical data from each of the jaundiced animals before and after bile duct ligation¹

The mean values are shown plus 1 standard error of the means.

brovascular response to noradrenaline and the degree of jaundice, or hepatic dysfunction as determined by any of the biochemical tests carried out. The plasma renin level was also not significantly altered in the jaundiced animals. Thus, we cannot identify any of these variables responsible for the alteration of cerebrovascular response to noradrenaline from normal.

Discussion

These findings indicate that in baboons following ligation of the bile duct there is an altered cerebrovascular response to infused noradrenaline. Cerebral vasoconstriction was obtained with infusions of noradrenaline at 8 μg and 16 μg in the jaundiced animals, whereas dilatation was evident in the control animals. These findings suggest an increased cerebrovascular sensitivity to noradrenaline in the obstructive jaundice following bile duct ligation.

Circulatory disturbances have been demonstrated in liver dysfunction, but the majority of the abnormalities described relate to a decreased peripheral resistance and abnormal cardiac output (Abramson and Lichtman, 1937; Kontos, Shapiro, Mauck, and Patterson, 1964; Martini and Hagemann, 1956; Huston and Puchner, 1957). In a recent study of renal blood flow in baboons with surgically induced obstructive jaundice, Bloom *et al* (1974) have shown that there is an increased vascular sensitivity to noradrenaline in this organ. In a further series of experiments Bloom *et al* (1975a) have demonstrated that plasma obtained from baboons with obstructive jaundice potentiates the effect of noradrenaline on an isolated femoral artery. This would imply that in obstructive jaundice there is some factor which increases the sensitivity of arterial smooth muscle to noradrenaline.

The effects of infused noradrenaline on the normal cerebral circulation have been intensively studied but no consistent pattern of response has emerged (Lassen, 1974). Reported results of infusion include cerebral vasoconstriction (Haggendal, 1965), vasodilatation (Sokoloff, 1959), or no effect (Olesen, 1972). Although much of this discrepancy may relate to the routes of administration and the anaesthesia used, other mechanisms may be operative. Rosenblum (1973) has suggested that the effectiveness of noradrenaline on cerebral vessels is reduced by avid neuronal uptake mechanisms, which prevent noradrenaline from reaching the receptor site in sufficient concentration to exert an effect. In support of this is the work of Rosendorff and Cranston (1971) who demonstrated cerebral vasoconstriction when noradrenaline was applied

locally in high concentration to the vascular surface. The latter result suggests a possible saturation of the neuronal uptake mechanism, allowing sufficient noradrenaline to reach the smooth muscle receptors.

These findings do not explain the lack of response to blood-borne noradrenaline which would be expected to reach the vascular muscle receptors before neuronal uptake (uptake 1) could be achieved. It is possible, however, that the blood-borne noradrenaline is avidly taken up by extraneuronal processes (uptake 2—Iversen, 1968) into the vascular smooth muscle. The noradrenaline is taken up into the smooth muscle cell and is there metabolized mainly by the enzyme catechol-o-methyl-transferase (Marley, 1964). Normally, the amount of noradrenaline taken up into the smooth muscle does not exceed the amount diffusing into the vascular wall from the blood. It has been shown that inhibition of the catechol-o-methyl-transferase enzyme slows down the uptake 2 processes making more noradrenaline available to the receptor and potentiates its effects (Kalsner, 1969). Conversely, if uptake 2 is very avid the effects of the noradrenaline would be reduced. McCalden and Eidelman (1975) have demonstrated that inhibition of catechol-o-methyl-transferase results in an enhanced cerebrovascular response to infused noradrenaline. These findings indicate that avid metabolism of noradrenaline within the vascular smooth muscle leading to an increased uptake 2 probably accounts for the normal relative lack of response of the cerebral vessels to noradrenaline.

The present findings of cerebral vascular constriction at low infusion rates of noradrenaline in jaundiced animals, as opposed to dilatation in the normal animals, are similar to those obtained by McCalden and Eidelman utilizing blockade by catechol-o-methyl-transferase. The dilatation observed in the normal probably relates to noradrenaline reaching the receptors in low concentration and exerting a primary beta adrenergic effect (Wahl, Koschinsky, Bosse, Olesen, Lassen, Ingvar, and Thureau, 1971/2). In the jaundiced animals the concentration of noradrenaline at the receptor sites is probably higher and this produces an alpha adrenergic stimulation resulting in vasoconstriction. This suggests that some factor or factors in the serum of animals with obstructive jaundice may be acting on vascular smooth muscle and inhibiting normal catecholamine uptake mechanisms.

The specific underlying factor or factors responsible for the enhanced responses to noradrenaline is speculative. In the kidney the changes in blood flow are not thought to be due to hyperbilirubinaemia (Spellberg, Sandlow, Allen, and Eshbaugh, 1963) although Baum, Sterling, and Dawson (1969),

using homozygous Gunn and Wistar rats, have implicated conjugated bilirubin as the agent which sensitizes the renal parenchyma to ischaemia. We could find no correlation between the serum bilirubin levels (direct or indirect), transaminase levels, enzyme levels and plasma renin levels, and the magnitude of the cerebral vasoconstrictor response following infusions of noradrenaline.

Aoyagi and Lowenstein (1968) have shown that infusions of bile salts sensitize the kidney to periods of ischaemia. Bile salts are steroids, and some steroids, such as oestrogens, are known to inhibit uptake 2 mechanisms (Iversen, 1968), which may explain the results obtained here. Salt and Iversen (1972) have shown that cholesterol is also capable of inhibiting uptake of noradrenaline into the heart muscle, and as there is an increase in cholesterol in obstructive jaundice (Sherlock, 1968) this may account for the present findings. This hypothesis is further reported by the finding of McCalden, Bloom, and Rosendorff (1975) that hypercholesterolaemic plasma is capable of potentiating the response of an isolated artery preparation to noradrenaline. Cholesterol may possibly be acting as an uptake 2 inhibitor, which would allow greater concentrations of noradrenaline to reach the vascular receptor and account for the vasoconstriction produced.

It may be argued that the cerebral pressor response to noradrenaline found in the present study is related to the prior bile duct surgery. We have conducted numerous experiments with animals which had undergone previous abdominal surgery and found that both the resting cerebral blood flow and the response of the cerebral vasculature to infused noradrenaline was identical to that in the control animals used here. Also the fact that resting cerebral blood flow, blood pressure and heart rate were little changed in the jaundiced animals would indicate that they had recovered from the trauma of surgery.

In our method the noradrenaline was infused through the carotid bifurcation before entering the internal carotid artery. It has been suggested that the bifurcation receptors are important in control of the cerebral vasculature (Ponte and Purves, 1974). Thus the present results may have been due to a reflex action on the cerebral vessels from these receptors. This we consider unlikely as other workers have not been able to repeat the observation of Ponte and Purves (Linton, Miller, and Cameron, 1975). McCalden and Eidelman (1975) have also found no change in the effect of infused noradrenaline when the bifurcation nerves are removed.

In conclusion these results show that in obstructive

jaundice there is an increased cerebrovascular sensitivity to noradrenaline similar to that found in the renal vasculature. We suggest that this hypersensitivity may be due to inhibition of uptake 2 mechanisms. No correlation was found between the degree of potentiation of noradrenaline and any of the plasma biochemical estimations. At present the constituents of the pathological plasma responsible for the potentiation have not been identified.

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References

- Abramson, D. I., and Lichtman, S. S. (1937). Influences of ergotamine tartrate upon peripheral blood-flow in subjects with liver disease. *Proc. Soc. exp. Biol. (N.Y.)*, 37, 262.
- Aoyagi, T., and Lowenstein, L. M. (1968). The effect of bile acids and renal ischemia on renal function. *J. Lab. clin. Med.*, 71, 686-692.
- Baum, M., Sterling, G. A., and Dawson, J. L. (1969). Further study into obstructive jaundice and ischaemic renal damage. *Brit. med. J.*, 2, 229-232.
- Bloom, D. S., Bomzon, L., Rosendorff, C., and Scriven, D. R. L. (1974). The effects of obstructive jaundice on renal blood flow. *Clin. Sci.*, 47, 3P-4P.
- Bloom, D. S., McCalden, T. A., and Rosendorff, C. (1975a). The effects of jaundiced plasma on vascular sensitivity to noradrenaline. In *Kidney International*. In press.
- Bloom, D. S., McCalden, T. A., and Rosendorff, C. (1975b). The effects of hypercholesterolaemic plasma on vascular sensitivity to noradrenaline. *Brit. J. Pharmacol.*, in press.
- Haggendal, E. (1965). Effects of some vasoactive drugs on the vessels of the cerebral grey matter of the dog. *Acta physiol. scand.*, 66, Suppl. 258, 55-79.
- Huston, J. H. and Puchner, T. C. (1957). Hemodynamics and myocardial oxygen consumption in decompensated portal cirrhosis. *Circulation*, 16, 896.
- Iversen, L. L. (1968). Role of noradrenaline uptake in adrenergic neurotransmission. In *Adrenergic Neurotransmission; CIBA Foundation Study Group*, No. 33, edited by G. E. W. Wolstenholme and M. O'Connor, pp. 44-59. Churchill, London.
- Kalsner, S. (1969). Mechanism of hydrocortisone potentiation of responses to epinephrine and norepinephrine in rabbit aorta. *Circulat. Res.*, 24, 383-395.
- Kontos, H. A., Shapiro, W., Mauck, H. P., and Patterson, J. L. (1964). General and regional circulatory alterations in cirrhosis of the liver. *Amer. J. Med.*, 37, 526-535.
- Lassen, N. A. (1974). Control of cerebral circulation in health and disease. *Circulat. Res.*, 34, 749-760.
- Linton, R. A. F., Miller, R., and Cameron, I. R. (1975). The effect of hypercapnia and carotid sinus nerve section on hypothalamic blood flow. In *Proceedings of the 7th International Congress on Cerebral Blood Flow and Metabolism*. Churchill, London. In press.
- McCalden, T. A., Bloom, D. S., and Rosendorff, C. (1975). Potentiation of the pressor effects of noradrenaline by jaundice and hypercholesterolaemia. In *Proceedings of the 2nd International Symposium on Vascular Neuroeffector Mechanisms in Blood Vessels*. In press.
- McCalden, T. A., and Eidelman, B. H. (1975). The cerebrovascular response to infused noradrenaline and its modification by a catecholamine metabolism blocker. In *Proceedings of the 7th International Congress on Cerebral Blood Flow and Metabolism*. Churchill, London. In press.
- Marley, E. (1974). The adrenergic system and sympathomimetic amines. *Advanc. Pharmacol.*, 3, 167-266.
- Martini, G. A. and Hagemann, J. E. (1956). Über Fingernagel

- veränderungen bei Lebercirrhose als Folge veränderter peripherer Durchblutung. *Klin. Wschr.*, 34, 25-31.
- Olesen, J. (1972). The effect of intracarotid epinephrine, norepinephrine and angiotensin on the regional cerebral blood flow in man. *Neurology (Minneapolis)*, 22, 978-987.
- Rosenblum, W. I. (1973). Increased binding of norepinephrine by nerves to cerebral blood vessels: evidence from the effects of reserpine on nerves to cerebral and extracerebral vessels. *Stroke*, 4, 42-45.
- Rosendorff, C., and Cranston, W. I. (1971). Effects of intrahypothalamic and intraventricular noradrenaline and SHT on hypothalamic blood flow in the conscious rabbit. *Circulat. Res.*, 28, 492-502.
- Salt, P. J., and Iversen, L. L. (1972). Inhibition of extraneuronal uptake of catecholamine in isolated rat heart by cholesterol.

- Nature [New Biol.]*, 238, 91-92.
- Sherlock, S. (1968). *Diseases of the Liver and Biliary System*, 4th ed., pp. 96-97. Blackwell, Oxford.
- Sokoloff, L. (1959). The action of drugs on the cerebral circulation. *Pharmacol. Rev.*, 11, 1-85.
- Spellberg, M. A., Sandlow, L. Allen, H., and Eshbaugh, D. (1963). Current concept of the hepatorenal syndrome: a clinico-pathologic study. *Geriatrics*, 18, 837-845.
- Strandgaard, S., MacKenzie, E. T., Sengupta, D., Rowan, J. O., Lassen, N. A., and Harper, A. M. (1974). Upper limit of autoregulation of cerebral blood flow in the baboon. *Circulat. Res.*, 34, 435-440.
- Wahl, M., Kuschinsky, W., Bosse, O., Olesen, J., Lassen, N. A., Ingvar, D. H., and Thurau, K. (1971/2). Adrenergic control of cerebral vascular resistance. *Europ. Neurol.*, 6, 185-189.

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