The influence of nimodipine on cerebral blood flow autoregulation and blood-brain barrier

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Twenty anesthetized rats were randomly assigned to a nimodipine-treated group or a control group of 10 rats each. Local cerebral blood flow (ICBF) was measured by means of a surface electrode using the hydrogen clearance technique. Systemic arterial pressure (SAP) was varied with administration of norfenefrine or by hemorrhage in order to obtain SAP/cerebral blood flow (CBF) curves under different conditions. In the control group, a typical autoregulation curve was obtained with an ICBF plateau between 70 and 120 mm Hg SAP. The nimodipine-treated animals, however, showed only a slight diminution in the slope of the curve but no real plateau, indicating impairment of CBF autoregulation. In another series, 20 anesthetized rats were randomly assigned to a treatment group or a control group of 10 animals each. Intravenous Evans blue dye was used as a tracer for blood-brain barrier (BBB) function. In both groups, SAP was raised to a level of 180 mm Hg with administration of norfenefrine for 6 minutes. Extravasation of significantly more Evans blue dye was observed in the nimodipine group than in the control group, indicating impairment of the BBB. It is concluded that nimodipine may impair CBF autoregulation, allowing damage to the BBB under hypertensive conditions.

KEY WORDS • nimodipine • cerebral blood flow • blood-brain barrier

TREATMENT with the calcium entry blocker nimodipine is recommended as effective therapy in cerebral vasospasm following subarachnoid hemorrhage (SAH). Clinical trials suggest a reduction of ischemic sequelae to 50% or less,1'16'24 and an increase in cerebral blood flow (CBF) was seen in nimodipine-treated patients with symptoms of vasospasm after SAH.7 On the other hand, treatment with hemodilution, hypervolemia, and induced hypertension is a widely accepted measure to reverse ischemic deficits caused by vasospasm.3,6,15,20 Although these two therapeutic regimens may have real benefits, there are nonresponders in both and the problem of cerebral vasospasm is still far from being solved.

This relative helplessness in treating a patient who is deteriorating from vasospasm might induce the physician to combine therapies that offer any promise of success. Thus, a combination of the two regimens — calcium antagonism and induced hypertension — may be considered. Hypothetically, it is possible that the benefit of one is abolished by adverse effects of the other or that a combination of both may be worse than no therapy at all.

Safety of induced hypertension presupposes an intact blood-brain barrier (BBB); if not, this therapy may promote edema.5 Continuity of the BBB during hypertension, on the other hand, depends on functioning CBF autoregulation,12,22 with the ability of cerebral vessels to keep CBF constant over a wide range of systemic arterial pressures (SAP's).

Autoregulation is provided by the contractility of vascular smooth muscles which depend on calcium, particularly in the cerebral vessels.11,19 The rationale of calcium antagonism is the prevention of vasospasm by blocking the entry of Ca++ into vascular smooth muscles and thus impairing their contractility. This impairment of smooth-muscle contractility not only may release cerebral vasospasm but it may also interfere with CBF autoregulation.

In order to investigate these factors, the influence of nimodipine on CBF autoregulation and the resulting effect on the BBB were studied under experimentally induced hypertension.

Materials and Methods

Cerebral Blood Flow Study

In the first study series, 20 Wistar rats weighing 250 to 280 gm each were randomly assigned to one of two groups of 10 rats each. Anesthesia was induced with
administration of ketamine (100 mg/kg body weight) and xylazine (20 mg/kg body weight), then maintained by repeated injections of ketamine (60 mg/kg every 30 minutes). The animals were tracheotomized, and the left femoral artery as well as both femoral veins were catheterized. The skull was fixed in a stereotaxic frame and the scalp was incised. A small lateral craniotomy was performed to 1 mm of the sagittal, coronal, and lambdoid sutures, reaching laterally 1 mm below the superior temporal line. The dura was opened using the microscope. All animals received 1 ml of a 6% solution of hydroxyethyl starch, with a molecular weight of 60 kD, to compensate for potential loss of volume during surgery. The SAP was monitored and CBF was determined as described below at various pressure levels. Variations in SAP were induced by infusion of norfenefrine (pressure increase) and by hemorrhage (pressure decrease).

The animals in the treatment group received a continuous infusion of nimodipine at a dose of 12 to 24 μg/kg/min for 15 minutes before measurements were made at different blood pressure levels. The dosage was adjusted within this range so only a slight decrease in blood pressure was observed.

The CBF was determined by the hydrogen clearance method. The ion-selective multiwire glass electrode* used for this technique contains platinum wires (diameter 100 μ) surrounded by a ring-shaped Ag/AgCl reference electrode (diameter 4 mm) (Fig. 1). This is placed directly on the brain surface with a counterbalance which allows only gentle contact in order to avoid any pressure on the tissue. It measures the local tissue hydrogen (H₂) concentration. For determinations of local CBF (ICBF), the animals are given a gas mixture containing 10% H₂ to inhale until a steady state is reached. They are then allowed to breathe room air, and the H₂ clearance curve is measured. This yields a nearly exponential function with the equation: \( c = c_0 \times e^{-Kt} \), whereby \( c \) is the actual hydrogen concentration at a given time, \( c_0 \) is the hydrogen concentration at the beginning of the measurement, \( e \) is Euler's constant, \( K \) is the slope of the curve, and \( T \) is the time in minutes. Since the tissue/blood partition coefficient of H₂ equals 1, the slope K of the curve is equivalent to the ICBF measured in ml/gm/min. As the clearance curve matched better with an exponential function when the first half-time had elapsed, the slope was calculated from the clearance curve over a period of 50 seconds, excluding the first half-time from evaluation.

**Blood-Brain Barrier Function Study**

In a second series, 20 rats were randomly assigned to a treatment or a control group of 10 rats each. Anesthesia and cannulation were performed as in the first series. Arterial pressure was monitored. In the treatment group nimodipine was infused at the same dosage as in the first series, and in the control group the animals received the fluid vehicle. After 15 minutes, Evans blue dye was injected intravenously at a dose of 5 mg/kg (2.5% solution in saline). The animals were allowed to compensate for the slight effect of the dye on the blood pressure, which consisted of a rise of about 20 to 40 mm Hg followed by a rebound effect with a decrease of 10 to 20 mm Hg from the starting point. About 20 minutes after the nimodipine or vehicle infusion was begun, the SAP was increased to 180 mm Hg. The increase was performed gradually by infusion of norfenefrine and took 2 to 3 minutes. Pressure peaks were avoided as well as a too-rapid increase in blood pressure. The level of 180 mm Hg was maintained for 6 minutes. The animals were then sacrificed with infusion of KCl solution, the aorta was cannulated, the vena cava was opened, and the animals were perfused with Ringer's solution.

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* Multiwire glass electrode manufactured by Eschweiler Co., Kiel, West Germany.
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<table>
<thead>
<tr>
<th>Animal Group</th>
<th>EB Staining</th>
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<td>3</td>
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<tr>
<td>placebo (vehicle)</td>
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<td>9</td>
</tr>
<tr>
<td>all animals</td>
<td>8</td>
<td>12</td>
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* EB = Evans blue dye: + = with; − = without. Results show a significant difference: χ² = 7.13, p < 0.01.

solution until the fluid from the caval vein became clear. The brains were removed and examined for Evans blue dye extravasation, then frozen in liquid nitrogen and stored at −30°C. 10-μ frozen brain sections were examined under a fluorescence microscope with a special filter for long-wave ultraviolet light which allowed detection of Evans blue dye fluorescence.

Results

Cerebral Blood Flow Findings

The control animals showed a typical CBF autoregulation curve with a lower limit of 70 mm Hg and an upper autoregulation limit of 130 mm Hg. Within this range the cortical ICBF was maintained at a level of about 120 ml/100 gm tissue/min (Fig. 2 lower). In the nimodipine-treated animals, the curve showed only a slight decrease in slope but no real plateau of the blood flow in the range in which autoregulation would be expected (Fig. 2 upper). The ICBF was increased markedly by nimodipine at all blood pressure levels above the lower autoregulation limit of 70 mm Hg. Interestingly, in three nimodipine-treated animals a sudden massive SAH was observed at a blood pressure of 150 mm Hg. In the control group only one hemorrhage occurred; this took place at a blood pressure of 200 mm Hg.

Blood-Brain Barrier Findings

In the second series, the animals pretreated with nimodipine showed more Evans blue dye extravasation than the animals pretreated with the vehicle. Only clearly visible Evans blue staining was recorded. This observation was significant by the chi-square test (Table 1). Evans blue dye could be detected as a distinct red fluorescence on the frozen sections. In animals pretreated with nimodipine, fluorescence microscopy revealed that the dye had left the endovasal space and had stained the vessel wall and the neuropil. In the control group, extravasation was not observed, or if so, only sporadically. The dye was mainly intravascular.

Discussion

The autoregulation curve of the control animals agrees well with data from the literature, especially with regard to the lower limit. 4,10,11,13,23 The upper limit in this study is less than the previously reported values of about 160 mm Hg. This may be explained by the use of ketamine as the anesthetic agent, because autoregulation depends upon various influences, including anesthesia. 8,16 Nevertheless, the values from the control group and from the nimodipine-treated animals can be compared because they were obtained under identical conditions except for the infusion of nimodipine. Our results show that nimodipine impairs CBF autoregulation.

Pretreatment with nimodipine also impairs the protective effect of autoregulation on the BBB. In our model a distinct extravasation of Evans blue dye was seen after 6 minutes of hypertension. The threshold above which a progressive BBB breakdown is to be expected is not known. Predictions of the effects of nimodipine on longer periods of hypertension cannot readily be concluded from our results; however, it is likely that these effects are more severe than those after only 6 minutes.

Based on these results, we are cautious in combining calcium entry blockers such as nimodipine with induced hypertension and hypovolemia in patients with clinical signs of vasospasm after SAH. We correct significant drops in SAP which are sometimes provoked by nimodipine but avoid increases in SAP above 155/95 mm Hg. Whether the concept of calcium antagonism or the treatment with hypertension and hypovole-
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References

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