TITLE: INDUCED HYPERTENSION DURING RESTORATION OF FLOW AFTER TEMPORARY MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT : EFFECT ON BRAIN INJURY AND EDEMA

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We have previously shown that phenylephrine induced hypertension, instituted immediately after or 2 hours after middle cerebral artery occlusion (MCAO) in the rat, results in a partial restoration of blood flow in the ischemic territory, together with a reduction in the extent of histochemical neuronal injury and ischemic edema. In the present investigation, the effect of induced hypertension instituted during restoration of flow after MCAO on neuronal injury, ischemic edema and blood brain barrier (BBB) permeability to macromolecules was studied. Under isoflurane anesthesia, the MCA of 12 spontaneously hypertensive rats was occluded using 10-0 Dermalon ligatures. Two hours following MCAO, the ligatures were released and flow was restored in both groups. In the control group (n=6), the mean arterial pressure (MAP) was not manipulated. In the hypertensive group (n=6), the MAP was gradually elevated by 25-30 mm Hg immediately after reestablishment of MCA patency. Four hours after MCAO, the rats were sacrificed and the brains were harvested. The brain were sectioned along coronal planes 1, 3, 5 and 7 mm from the frontal pole; these sections span the distribution of ischemia produced by MCAO. The block of tissue between the 3-5 mm planes was used to determine specific gravity (SG) in the subcortex and in two sites in the cortex (lateral and dorsal cortex). The extent of neuronal injury was determined by 2,3,5-triphenyltetrazolium (TTC) staining in the two blocks of tissue between the 1-3 mm and 5-7 mm planes. In 4 rats, 2 in each group, 1 ml/kg of 3% Evans Blue was injected half an hour prior to sacrifice. The brains were harvested and sliced as described above. In both groups, hypertension (H) and control (C), the SG was lower in the left hemisphere (ipsilateral to MCAO) than in the right hemisphere. In the left hemisphere, the SG in the subcortex (1.040 ± 0.002 vs 1.042 ± 0.001, n.s.), lateral cortex (1.038 ± 0.001 vs 1.039 ± 0.001, n.s.) and dorsal cortex (1.042 ± 0.001 vs 1.042 ± 0.001, n.s.) was not different in the two groups (control vs hypertension groups respectively). The area of histochemical injury (as a percentage of the cross sectional area of the hemisphere in the coronal plane) in the 3 mm plane (31% ± 2 vs 18% ± 2, $p<0.05$) and in the 5 mm plane (30% ± 3 vs 20 % ± 1, $p<0.05$) was significantly lower in the hypertensive group. Evans Blue extravasation into the brain parenchyma was not seen in either group.

The data show that hypertension instituted during restoration of flow 2 hours after MCAO does not aggravate ischemic edema, reduces the extent of histochemical neuronal injury and does not result in an opening of the BBB to macromolecules. The therapeutic window during which induced hypertension will not aggravate edema even in the event of reestablished vessel patency is at least two hours in this model.

TITLE: ROLE OF BENZODIAZEPINE RECEPTOR SYSTEM IN BENZODIAZEPINE-BARBITURATE ANESTHETIC SYNERGISM

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Profound benzodiazepine-barbiturate anesthetic synergism was explained by allosteric modulation of benzodiazepine receptors.[1] At the same time there are data suggesting that part of the benzodiazepine-induced anesthetic effect is the result of an action at a site other than the benzodiazepine receptor.[2] The aim of the present study was to determine whether flumazenil, a benzodiazepine receptor antagonist, can completely reverse the potentiating effect of midazolam on pentobarbital-induced anesthesia.

Male Sprague-Dawley rats (225-275g) were used for the study, which was approved by the Institutional Animal Investigation Committee. Loss of the righting reflex was used as an index of hypnotic action. In five series of experiments a pentobarbital dose-response curve was determined (probit analysis) with and without (vehicles only) interacting drugs indicated in the table.

The hypnotic ED_{50} value for pentobarbital was profoundly decreased (2.8 mg·kg^{-1}, vs 9.7 mg·kg^{-1}, $p<0.001$) by midazolam used in a dose (0.3 mg·kg^{-1}) which represents only 5% of the midazolam hypnotic ED_{50} value. The midazolam-induced change in the pentobarbital ED_{50} value was reversed with flumazenil 3 mg·kg^{-1} (8.4 mg·kg^{-1} vs. 2.8 mg·kg^{-1}, $p<0.001$). The effect of flumazenil 10 mg·kg^{-1} was not significantly different from that of flumazenil 3 mg·kg^{-1}. The complete reversal of the potentiating effect of midazolam on the pentobarbital-induced hypnosis suggests that the sites other than the benzodiazepine receptors do not play any significant role in this effect.

REFERENCES: 1. Anesth Analg 67:342-5, 1988. 2. Br J Anaesth 56:1153-9, 1984.

Table. Flumazenil-Midazolam-Pentobarbital Interaction

Series	Interacting drugs	Pentobarbital ED_{50} mg·kg^{-1}, i.v. (95% conf. limits)	Potency ratio
A	None	9.7 (4.9, 12.2)	1.00
B	Midazolam 0.3 mg·kg^{-1}, i.v.	2.8 (1.8, 3.8)	3.46 p<.001*
C	Midazolam 0.3 mg·kg^{-1}, i.v. Flumazenil 3 mg·kg^{-1}, i.p.	8.4 (7.3, 10.3)	1.15 NS*
D	Midazolam 0.3 mg·kg^{-1}, i.v. Flumazenil 10 mg·kg^{-1}, i.p.	8.5 (6.5, 11.0)	1.14 NS*
E	Flumazenil 10 mg·kg^{-1}, i.p.	10.4 (7.9, 12.3)	0.93 NS*

* From A.