The Effects of Intraventricular Administration of Norepinephrine on Vasogenic Edema

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Abstract

The effects of intraventricular application of norepinephrine (NE) on the development of vasogenic edema was studied in mongrel dogs randomly divided into a control and an experimental group (NE group). Vasogenic edema was produced by infusion of a 2.0 M NaCl solution (hypertonic saline) unilaterally into the carotid artery. NE (40μg⁄kg) was injected into the lateral ventricle 30 minutes before the infusion of hypertonic saline, after which intracranial pressure (ICP) and systemic blood pressure were continuously recorded. The animals were sacrificed 2 hours after the infusion of hypertonic saline and brain tissues were sampled from both hemispheres for measurement of the water content. Infusion of hypertonic saline produced a marked increase in ICP in the control group and a lesser increase in the NE group. The mean ICP in the control group was significantly higher (p < 0.01) than that of the NE group from 30 to 120 minutes after saline infusion. The water content of the saline-infused hemisphere was significantly higher than that of the contralateral hemisphere in the control group, whereas the difference was not significant in the NE group. These results suggest that intraventricular administration of NE may protect against the development of intracranial hypertension due to vasogenic edema.

Key words: intracranial hypertension, norepinephrine, vasogenic brain edema, blood-brain barrier

Introduction

The classification of brain edema introduced by Klatzo, which includes vasogenic and cytotoxic edema, is widely accepted. Vasogenic edema is described in pathophysiological terms as the extravasation of macromolecules and accumulation of fluid in the extracellular spaces, which results from the breakdown of the blood-brain barrier (BBB). Vasogenic edema is produced by brain tumors, head injury, and brain inflammation and often leads to intracranial hypertension, with a potential risk of brain herniation. Several therapeutic means of decreasing the elevated intracranial pressure (ICP) or preventing further development of vasogenic edema have been investigated. Hayashi et al. proposed that norepinephrine (NE) may have the effect of reducing intracranial hypertension. However, although the cerebral circulatory response to NE has been the subject of many investigations, the findings have been inconsistent. The purpose of this study was to assess the effects of intraventricular administration of NE on vasogenic edema produced by infusion of a hyperosmotic agent into the cerebral circulation.

Materials and Methods

Mongrel dogs weighing 7.5–10 kg were randomly divided into a control group (n = 10) and an intraventricular NE treatment group (NE group) (n = 10). The animals were cared for in accordance with the guidelines of the Japan Science Council on Animal Experimentation. They were anesthetized by intravenous administration of sodium thiopental (5 mg/kg/hour) and paralyzed by intravenous infusion of pancuronium bromide (0.05 mg/kg/hour). All animals were intubated and artificially ventilated with room air. Blood gas analysis was performed to adjust and maintain PaCO2 at 35–40 mmHg. The depth of anesthesia was monitored by cortical electroencephalography (EEG). ICP was recorded...
through a needle inserted into the lateral ventricle and connected to a pressure transducer (Model P-50, Gould Statham, Oxnard, CA, USA). Systemic blood pressure (SBP) was recorded through a catheter inserted into the abdominal aorta via the femoral artery. A physiological saline solution was continuously infused into the lateral ventricle through a needle to maintain ICP at 15–20 mmHg.

Vasogenic edema was produced by the infusion of a 2.0 M saline solution into the internal carotid artery on one side. The lingual artery was ligated and the hypertonic solution (1 ml/kg) was infused into the internal carotid artery in 1 minute via a catheter inserted into the thyroid artery. ICP, SBP, and cortical EEG were continuously recorded from the bilateral parietal regions, during and for 120 minutes following infusion of the hypertonic saline solution.

In the NE group, 0.1 ml of NE (40 μg/kg) was injected into the lateral ventricle ipsilateral to the cannulated thyroid artery 30 minutes prior to the beginning of the hypertonic saline infusion. To evaluate the extent of vasogenic edema, a 2% solution of Evans blue dye was injected intravenously (2 ml/kg) in all animals prior to intracarotid infusion of hypertonic saline. Two hours after the start of the hypertonic saline infusion, the animals were sacrificed by intravenous injection of a large dose of sodium thiopental followed by KCl. The brain was removed immediately and cut in the coronal plane through the pituitary gland. Extravasation of Evans blue was examined macroscopically on the coronal brain section. Brain tissues were sampled from eight anatomical regions of the caudal portion of the cut brain: the bilateral temporal and parietal gray matter, parietal white matter, and caudate nucleus. The water content of these brain samples was determined by the dry weight method. The rostral part of the brain was fixed in a 4% formaldehyde solution for 1 month, then dehydrated and embedded in wax. Sections of brain 8 μm in thickness were prepared and stained with HE. The mean ICP, SBP, and cerebral perfusion pressure (CPP) of the two groups before and every 30 minutes after the hypertonic saline infusion were compared. The water content of the saline-infused and contralateral hemispheres was evaluated in all animals.

The data were analyzed by Student's t-test. P values of 0.05 or less were regarded as statistically significant. Analysis of variance was used for inter- and intragroup comparisons.

Results

I. ICP, SBP, and CPP changes

There was no significant difference in mean ICP between the two groups prior to hypertonic saline infusion. In both groups, mean ICP increased after saline infusion. The increase in the NE group, however, was significantly (p < 0.01) smaller than that in the control group (Fig. 1). There were no significant differences in either mean SBP or CPP between the two groups, before or after saline infusion.

Figure 2 shows SBP and ICP recordings from a representative control dog and the NE animal. In control dog, intracarotid infusion of hypertonic
saline produced a marked increase in ICP and a concomitant decrease in SBP. The mean ICP peaked between 30 and 45 minutes after saline infusion, and the ICP gradually decreased thereafter. In the NE animal, infusion of hypertonic saline produced a small increase in mean ICP compared with that observed in the control group.

II. Water content
In the control group, the water content of brain tissues sampled from the parietal white matter, temporal gray matter, and caudate nucleus was significantly higher (p < 0.05) in the ipsilateral hemisphere than in the contralateral hemisphere, whereas the water content showed no significant interhemispheric differences in the parietal gray matter. In the NE group, on the other hand, there were no significant interhemispheric differences in the water content of any of the brain regions examined (Fig. 3).

III. Dye extravasation
In the control group, extravasation of dye was obvious in the parietal white matter and the temporal gray matter of the ipsilateral hemisphere, but was negligible in the contralateral hemisphere. In the NE group, there was little or no extravasation of dye in either hemisphere.

IV. Microscopic findings
Under microscopic observation, the brain specimens exhibited the features of vasogenic edema, particularly in the parietal white matter in the hypertonic saline-infused hemisphere of the control group (Fig. 4). Edema was minimal in the contralateral...
intraventricular NE (40µg/kg) was required to elicit that the BBB could be disrupted by infusion of a hemisphere in the control group and in both hemispheres in the NE group.

**Discussion**

That the BBB could be disrupted by infusion of a hyperosmotic solution into the cerebral circulation was demonstrated by Rapoport et al.\(^{19}\) The increase in permeability produced by osmotic treatment is probably caused by shrinkage of endothelial cells and widening of the tight junctions. However, Houthoff et al.\(^{9}\) reported that osmotic injury appears to induce an increase in pinocytotic activity and, possibly, opening of the transendothelial channels. The results of studies involving experimental brain edema suggest that the water content is the true index of brain edema, and in fact there is a strong correlation between the water content and extravasation of Evans blue dye in vasogenic edema.\(^{2}\) In our study, we used the water content measured in various brain tissues as a numerical index of vasogenic edema and observed the extravasation of dye in order to evaluate the extent of BBB disruption. In the control group, the increase in water content and the extent of Evans blue dye extravasation were positively correlated.

MacKenzie et al.\(^{12}\) reported that a large dose of intraventricular NE (40µg/kg) was required to elicit increases in cerebral blood flow, cerebral oxygen consumption, and cerebral glucose uptake. Feldberg and Sherwood\(^{30}\) found that intraventricular injection of 40µg/kg of NE produced marked alterations in cat behavior, while 5µg/kg did not. In this study, therefore, we administered a large dose of NE (40µg/kg) intraventricularly. Mcllwain and Bachelard\(^{33}\) stated that NE or epinephrine intraventricularly or intracisternally, have some effects, such as increasing blood glucose levels, but that anesthesia may occur. They also noted that SBP and heart rate do not increase. In our study, there were no significant differences in mean SBP or CPP between the control and NE groups, either before or after saline infusion. Durward et al.\(^{39}\) reported that injection of hypertonic saline into the carotid artery resulted in rapid edema formation, and the increase in CPP caused marked extravasation of Evans blue dye. In our study, however, although changes in CPP after hypertonic saline infusion did not differ significantly between the control and NE groups, the increases in brain water content and ICP were significantly greater in the controls than in the NE group. These results suggest that intraventricular NE administration protects against intracranial hypertension due to by vasogenic edema.

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Studies of the influence of peripheral sympathetic nerves on cerebral circulation\(^{4,14}\) have shown that sympathetic discharge causes vasoconstriction of extraparenchymal resistant vessels, which implies sympathetic regulation of cerebral blood flow. Moreover, this vasoconstrictive effect is more pronounced when ICP is extremely elevated. The possibility of central noradrenergic regulation of cerebral blood flow and vascular permeability was proposed by Raichle et al.\(^{16}\) In their experiments, stimulation of noradrenergic cell bodies in the locus coeruleus produced a prompt reduction in hemispheric blood flow and an increase in brain vascular permeability. Grubb et al.\(^{7}\) reported that stimulation of peripheral sympathetic nerve fibers resulted in a significantly larger increase in brain water permeability than was achieved by locus coeruleus stimulation. These results indicate that the cerebral vascular bed may be controlled by both the peripheral and central noradrenergic systems. Thus, the permeability of the cerebral microvasculature may be regulated by not only the peripheral but also the central noradrenergic systems. In our study, NE demonstrated a protective effect against the increase in bulk water permeability caused by disruption of the BBB. On the other hand, Raichle et al.\(^{16}\) found that stimulation of adrenergic neurons, which is thought to release norepinephrine at the effector site, increased labeled water permeability. We believe this discrepancy concerning the effect of NE on vascular permeability to be attributable to physiological differences in the cerebral microvasculature of the subjects in these two studies and/or to differences between labeled and bulk water permeability.

Direct administration of NE into the perivascular space around the pial arteries leads to vasoconstriction.\(^{10}\) On the other hand, Olesen\(^{19}\) and Wahl et al.\(^{18}\) have shown that intravascular administration of NE has little or no effect on cerebral blood flow because catecholamines cannot cross the BBB.\(^{19}\) It is recognized that NE applied directly to the ventricular system apparently crosses the ependyma and increases both cerebral blood flow and utilization of oxygen and glucose.\(^{10,12}\) Carr and Moore\(^{11}\) reported that, in cats, labeled NE concentrated mainly in the caudate nucleus and hypothalamus when injected into the lateral ventricle, and mainly in the hypothalamus and brainstem when injected into the third ventricle. This suggests that an elevation of the concentration of NE in the cerebral interstitial fluid through its intraventricular administration may affect cerebral blood flow and metabolism in at least two ways: indirectly through the brainstem and directly in the paraventricular tissue. The results of our study sug-
gest the possibility that exogenous NE affects not only the paraventricular regions but also the cerebral vessels in the subarachnoid space, via cerebrospinal fluid flow, because the NE dose that we used was high relative to that employed by Carr and Moore.¹¹

In summary, the results of this study suggest that intraventricular administration of NE may protect against intracranial hypertension due to vasogenic edema. NE possibly has a direct vasoconstrictive effect on pial vessels and also may contribute to the normalization of the water permeability of microvessels via the central noradrenergic system. In addition, we speculate that intraventricular NE administration may not only protect against the development of vasogenic edema but also may be of value in the treatment of the edema.

References


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