Role of histamine in posttraumatic spinal cord hyperemia and the luxury perfusion syndrome

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The authors studied the effect of pretreatment of monkeys with antihistamines on hyperemia observed in the lateral funiculus of the spinal cord after severe experimental spinal cord trauma. After administration of Chlorpheniramine and Metiamide, the spinal cords were traumatized with a 600 gm-cm injury. Blood flow in the lateral funiculus at the injury site was then determined hourly for 6 hours. The blood flow at this site remained in the normal range at all times in all animals. Neither a hyperemia nor an ischemia could be demonstrated. This finding reaffirms the authors’ previous observation that ischemia does not exist in the lateral funiculus after severe experimental spinal cord trauma, and explains the previous observation of hyperemia as a histamine-related phenomenon, easily blocked by the administration of Chlorpheniramine and Metiamide, potent antihistamines which together block both the H₁ and H₂ receptor sites.

KEY WORDS - histamine - luxury perfusion syndrome - spinal cord injury

In earlier experiments we demonstrated hyperemia in the lateral funiculus after severe experimental injury to the spinal cord.⁸,¹³,¹⁴ This finding contradicted previous theories of a progressive ischemia as the etiological factor responsible for the observed neural dysfunction.²⁰ Prompted by a previous report of elevated histamine levels of the injured spinal cord segment after trauma,¹⁹ we explored the possibility in this study that the hyperemia observed in our previous experiments was a histamine-related phenomenon.

Methods and Materials

Five adult rhesus monkeys, unselected as to sex, were anesthetized with Ketamine and atropine. Catheters were inserted into the femoral vein for fluid replacement and the administration of drugs, and into the femoral artery for continuous blood pressure monitoring and periodic blood gas sampling. The animals were then intubated, curarized with Pancuronium, and placed on a volume respirator, receiving N₂O and O₂ in a 2:1 mixture for the remainder of the experiment.
Blood gases were frequently obtained and kept in the physiological range. Rectal temperature was maintained at 37° to 39°C. A heating pad was used when necessary.

The animals were then given 3 mg/kg Chlorpheniramine and 0.7 mg/kg Metiamide intravenously. Metiamide was continuously infused intravenously at a rate of 2.44 mg/kg/hr for the remainder of the experiment.

A standard mid-dorsal laminectomy was then performed, exposing the dura-covered spinal cord from T8-11. The spinal cord was then traumatized with a 600 gm-cm injury as previously described. A platinum electrode, 250 μ in diameter, was then placed into the lateral funiculus as described in earlier reports. The hydrogen clearance method was used, and blood flow determinations were obtained every half hour or hour for 6 hours after injury.

Blood flow determinations were obtained in the same manner as in earlier publications. The blood flow is calculated from the monoexponential tissue desaturation curve of previously inhaled hydrogen gas. It should be emphasized that this method measures focal blood flow in a discrete volume of tissue surrounding the electrode tip, less than 0.5 cu mm. At the end of the experimental period, the animals were sacrificed, and the injured spinal cord segment removed.

In three additional control animals, multiple blood flow determinations in the lateral funiculus were obtained under normotensive, normocapnic, normothermic conditions, both before and after the administration of antihistamines, given at the same dosage schedule as the experimental animals received. This was done to ascertain the effect, if any, of antihistamines on spinal cord blood flow under physiological conditions.

**Results**

As in previous experiments, the systemic arterial blood pressure rose immediately after injury. This rise however, was transitory, and only lasted for 60 to 90 seconds before the arterial pressure returned to the normal range. The blood flow in the lateral funiculus remained in the normal range at all times in all traumatized animals (Fig. 1). Neither a hyperemia nor an ischemia was observed. At postmortem examination, all of the spinal cords from the traumatized animals demonstrated the well-known central hemorrhagic lesion at the injury site, unchanged in appearance from those preparations that did not receive antihistamines.

Blood flow measured in the lateral funiculus of the control animals did not significantly change after the administration of antihistamines, and remained in the normal range during the 3-hour period of measurement.

**Discussion**

The pathophysiology of experimental spinal cord injury that is responsible for the associated neural dysfunction is still not well understood. In the last several years, Osterholm's theory of a catecholamine-mediated spreading ischemia of the white matter has been seriously questioned. Other laboratories have not been able to substantiate the finding of elevated norepinephrine levels of the injured spinal segment. We demonstrated a hyperemia, rather than ischemia, in the lateral white matter following experimental injury sufficient to render the animal permanently paraplegic. Griffiths and Miller have also shown adequate perfusion at all times in the lateral white matter of canine spinal cord after severe experimental trauma.
Our initial reaction to our observed hyperemia was that the injury may interfere with the mechanism of autoregulation, which we have shown exists in the spinal cord, and follows a pattern similar to that observed in the brain.\textsuperscript{7,9,10} Certainly this would explain the hyperemia, namely, after injury the blood flow would become passively controlled by the systemic arterial pressure. This finding would also be consistent with some theories proposed to explain the same phenomenon observed in the brain, in an area surrounding a cerebral infarct or traumatized cerebral tissue: the so-called “luxury perfusion syndrome.”\textsuperscript{11,21}

However, it was interesting to note that in an experiment by Naftchi, \textit{et al.},\textsuperscript{19} which failed to show any significant rise in norepinephrine levels of the injured spinal cord segment after trauma, histamine levels doubled. Histamine has been shown to increase blood flow in tissue through which it is perfused. This effect is based on loss of tone of the precapillary arterioles and capillaries, which results in vasodilatation and increased flow.\textsuperscript{4}

In light of this observation, the findings of the present experiment tend to explain the previously observed hyperemia as a histamine-related phenomenon, easily blocked by the administration of Chlorpheniramine and Metiamide, which together block both the H\textsubscript{1} and H\textsubscript{2} receptor sites. We chose to use this combination of antihistamines in this experiment to obtain the maximal antihistaminic effect. Blockage of the H\textsubscript{2} receptor site has been found necessary to block other histamine-related phenomena such as gastric secretion and histamine-induced hypotension.\textsuperscript{3,17} An ongoing experiment has been designed to learn if the hyperemia will be blocked with H\textsubscript{1} or H\textsubscript{2} blockage alone.

The largest supply of histamine in the body is manufactured and stored in the mast cell. The greatest concentration of these cells is in the skin and subcutaneous tissue.\textsuperscript{23} Histamine is released from mast cells under various conditions, one of which is trauma. Mechanical stimulation, that is, pinching and pricking of isolated pieces of skin, has resulted in histamine release, with the amount liberated directly proportional to the degree of trauma.\textsuperscript{24}

Although mast cells have been demonstrated in the dura mater, they have not been found in any significant numbers in the central nervous system (CNS) parenchyma.\textsuperscript{23} Nevertheless, biological assay of nervous tissue reveals a significant concentration of histamine, asymmetrically distributed within the nervous system, more concentrated in the gray matter than in the white.\textsuperscript{25} Its presence in the CNS is evidence to most investigators that histamine is a biologically active amine, although its exact role in the CNS remains unclear.\textsuperscript{1,23} The formation of histamine from histidine by brain tissue has been demonstrated \textit{in vitro} in various animal models, and it is felt, therefore, that the histamine measured in the CNS is manufactured and stored there.\textsuperscript{6}

Histamine is also normally present in the blood, stored in both leucocytes and platelets.\textsuperscript{23} Blood histamine levels have been shown to rise after generalized, as well as localized, trauma to a single limb or section of the body.\textsuperscript{18}

The rise in histamine levels of the injured spinal segment demonstrated by Naftchi is most probably explained by two mechanisms: 1) release of histamine from the injured neurons in the central gray matter of the injured segment, which could then diffuse into the surrounding white matter causing vasodilatation and increased blood flow; and 2) an increase in the blood histamine level secondary to trauma, either local or generalized, which results in increased amounts of histamine “leaking” into the central hemorrhagic lesion, and subsequently diffusing into the surrounding white matter.

Since histamine has been shown to increase vascular permeability as well as tone,\textsuperscript{2} it may also be implicated in the development of edema in the peripheral white matter which follows experimental trauma. In the situation described above, the hyperemia observed in our previous experiment would contribute to the edema formation. We are attempting at present to quantitate the amount of post-traumatic edema in the lateral white matter to ascertain the effect of antihistamines on this phenomenon.

Are the results of this experiment applicable to similar phenomena observed in other parts of the CNS? It has been known since 1966, when Lassen first described the luxury perfusion syndrome, that conditions can occur in the brain where an actual or relative hyperemia can exist on the fringe of
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ischemic brain tissue. Other investigators have shown that a similar condition can exist around a localized area of trauma in the brain. The pathology of experimental spinal cord injury has been relatively well documented. By 4 hours after injury, a grossly visible hemorrhagic lesion of the center of the cord is present. Whether this central lesion is secondary to the direct effects of trauma, or to the release of some as yet unknown substance, is not clear. However, the situation that develops, namely a hyperemia in the white matter surrounding this lesion, is comparable to the analogous situation in the brain. Further studies are necessary to determine if histamine or histamine-like substances are involved in the development of the luxury perfusion syndrome in these other situations.

Summary

In a previous experiment we demonstrated a hyperemia in the lateral funiculus of the monkey spinal cord after severe experimental spinal cord trauma. In this experiment we have studied the effect of pretreatment of the animals with antihistamines on the previously observed hyperemia. After administration of Chlorpheniramine and Metiamide, the spinal cords of monkeys were traumatized with a 600 gm-cm injury. Blood flow in the lateral funiculus at the injury site was then determined for 6 hours.

The blood flow at this site remained in the normal range at all times in all animals. Neither a hyperemia nor an ischemia could be demonstrated. This finding reaffirms our previous observations that ischemia does not exist in the lateral funiculus after severe experimental spinal cord trauma, and explains our previous observation of hyperemia as a histamine related phenomenon, easily blocked by the administration of Chlorpheniramine and Metiamide, potent antihistamines which together block both the H₁ and H₂ receptor sites.

This phenomenon may be applicable to injury in other parts of the central nervous system, and may play a role in the development of the luxury perfusion syndrome which has been shown to be present at the periphery of a cerebral infarction of traumatized cerebral tissue.

References


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This study was supported in part by grants from the U.S. Army Medical Research and Development Command.

This paper was presented in part at the Annual Meeting of the American Association of Neurological Surgeons, on April 9, 1975, at Miami, Florida.

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