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The Effects of Hypertonic Saline on Spinal Cord Blood Flow Following Compression Injury

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Summary

7.5% hypertonic saline was administered following spinal cord injury to test its effect on spinal cord blood flow. Four different groups of rats underwent 10 minutes of spinal cord compression (45g) at the C3 to C5 levels. A fifth group was not injured, but received hypertonic saline (5 ml/kg) at 5, 15 and 60 minutes following injury. Somatosensory evoked potentials and spinal cord blood flow were measured prior to and for 4 hours following the injury. The administration of hypertonic saline caused a significant increase in flow when administered 5 minutes following injury. Topical nitroprusside administration did not cause any increase in spinal cord blood flow during this time period. Hypertonic saline administration at the later time periods did not increase spinal cord blood flow. The group of animals which were not injured, but received hypertonic saline also showed no significant change in flow. The somatosensory evoked response of the treated animals was maintained for 4 hours after the injury where as the untreated animals began to lose their evoked responses 3 hours after injury.

Keywords: Spinal cord; hypertonic saline.

Introduction

During the last decade, it has become apparent that pathological changes resulting from trauma to the spinal cord are a result of both the initial primary mechanical damage (compression, contusion, etc.) and secondary pathological changes [2, 25]. There are many factors which have been postulated to contribute to secondary injury such as free radical lipid peroxidation [1, 4], membrane lipid changes [4] and decreased microvascular perfusion [6, 18, 21, 24].

A better understanding of the factors contributing to secondary injury is still needed. Our laboratory has previously studied flow changes following compression injury [27, 30]. We found that following administration of hypertonic saline after compression, spinal cord blood flow was enhanced and this increase was not merely due to an increased blood volume. The purpose of the present investigation was to better understand the effects of hypertonic saline on spinal cord blood flow. Hypertonic saline was administered to animals at various time periods following a compression injury to the spinal cord and spinal blood flow and electrophysiological responses were monitored for 4 hours after injury.

Methods

All experiments were conducted in accordance with and approved by the Animal Care and Use Committee at Temple University. Sprague Dawley rats weighing between 225–300 grams were used in this study.

Anesthesia was induced using methohexital sodium (50 ug/kg i.p.) (Eli Lilly & Co., Indianapolis, IN) and maintained using a bolus dose of Fentanyl citrate (50 ug/kg i.v.) (Abott Laboratories, North Chicago, IL) followed by a constant infusion of fentanyl citrate (100 ug/kg/h.i.v.) A tracheotomy was performed and both femoral veins and arteries were catheterized and mean arterial blood pressure was monitored (Grass Instruments, Quincy, MA). Body temperature was measured using a rectal probe (YSI, Yellow Springs, Ohio) and maintained at 37 °C through the use of a heat lamp.

The animals were paralyzed using pancuronium bromide (2 mg/kg i.v.) (Astra Pharmaceutical Products Inc., Westborough, MA) and ventilated (Harvard Apparatus, Sough Natick, MA) on 100% oxygen. The pCO_2 was maintained at a mean of $41.4 + 4.8$. A constant infusion of bicarbonate (American Regent Lab. Inc., Shirley, NY) was administered (84 mg/kg/h i.v.) to maintain pH and atropine (Elkins Sinn Inc., Cherry Hill, NJ) was administered (40 ug/kg i.m.) to decrease bronchial secretions.

Prior to the laminectomy, the animal's head was fixed in a stereotactic device. A midline incision was made and the laminae were exposed. A drill was used to perform the laminectomy (C3 to C5), and the dura remained intact. Once the spinal cord was exposed, it was bathed in artificial cerebral spinal fluid warmed to 37 °C and a needle probe (YSI, Yellow Springs, OH) was placed in the surrounding tissue to monitor temperature. A heat lamp was used to maintain the spinal cord temperature at 37 °C.

The injury was induced using a 5×2 mm footplate with edges

curved to conform to the shape of the spinal cord that was gently positioned over the cord using a micromanipulator.

The injury was induced by placing 31 grams of weight on a compression device for 10 minutes. The total weight resting on the spinal cord was 45 grams.

A laser Doppler flow probe (0.84 mm diameter) (TSI, St. Paul, MN) was then placed above the exposed spinal cord to monitor changes in spinal cord blood flow. To briefly describe the measurement technique, when the fiberoptic probe was placed over the perfused tissue, the emitted photons collided with moving red blood cells and stationary tissue. Only those photons that are scattered by the moving red blood cells undergo a Doppler frequency shift. A photodetector that uses the fiberoptic probe to collect the scattered photons, converts the reflected Doppler frequency spectrum into an analog voltage signal. This signal is fed through an analog to digital converter and digitized. This digitized signal is analyzed by a 16 bit microprocessor. This technique provides continuous online measurement of flow, but does not allow measurement of absolute blood flow values. However, the laser Doppler technique has been shown to correlate very closely with the radioisotope labeled microsphere technique in the assessment of changes in flow [5]. Care was taken to place the probe over an area without large blood vessels. The laser Doppler technique has been shown to give falsely elevated readings if placed over large vessels. Care was also taken not to compress the cord while placing the probe. Blood flow was monitored prior to injury and for the duration of the experiment following injury.

Somatosensory evoked potentials (SSEPs) were monitored using a technique extensively utilized by our laboratory [28, 30]. Platinum needle electrodes were placed subcutaneously for field stimulation of the median nerve in the foreleg.

Electrical stimuli were delivered at a frequency of 4 Hz with a duration of 0.1 ms and a voltage of 8–10 V. Electroencephalographic activity was recorded from the C3, Fz electrode position corresponding to the somatosensory area of the cortex contralateral to the stimulated side. The information was fed through an analogdigital (A–D) converter to a computer for analysis. A baseline SSEP using percutaneous median nerve stimulation was obtained prior to any surgical procedure. The animals were divided into 5 groups ($n = 5$ in each group) and randomly allocated among the groups. The animals in the sham group were not injured, but received hypertonic saline to test the effect of hypertonic saline on the uninjured spinal cord. The untreated group received no treatment after the compression injury. All treated groups received 5 ml/kg of 7.5% hypertonic saline. The 5 minute group received hypertonic saline 5 minutes following injury. The 15 minute and 60 minute groups received hypertonic saline 15 minutes and 60 minutes following injury, respectively.

Somatosensory evoked potentials were measured at 5, 10, and 15 minutes following injury for the first 30 minutes and then every 30 minutes up to 4 hours. The somatosensory evoked potentials were evaluated for the presence of a positive cortical peak and analyzed by evaluators who were blinded as to the treatment of the animals. Spinal cord blood flow was measured continuously prior to and following the injury. The data were analyzed using an analysis of variance and a tukey test for post hoc analysis where applicable. When two groups were being compared, a student t-test was used ($p < 0.05$).

Two separate groups of animals were used to evaluate the changes in spinal cord blood flow following topical nitroprusside application (Sigma Chemical Co, St. Louis, MO).

In the first group of uninjured animals ($n = 5$), the dura was carefully opened as to not damage the spinal cord. The flow probe was placed above the spinal cord. A volume of 0.5 m–1.0 ml of a 1% nitroprusside solution was applied topically and the flow changes were observed. In the second group, the animals were injured ($n = 5$) and following the injury, the dura was carefully opened. At 10 minutes following the injury, nitroprusside was applied topically to the cord in the same concentration as in the uninjured animals and the flow changes were observed in these animals. In both the injured and uninjured animals, a 7.5% hypertonic saline solution was administered i.v. (5 ml/kg) following nitroprusside application. Statistical analysis was performed using analysis of variance and a tukey test for post hoc analysis where applicable ($p < 0.05$).

Results

Figure 1 represents the changes which occur in spinal cord blood flow following spinal cord injury in animals which are not treated with hypertonic saline. The flow was initially increased following injury to a maximum flow of 46% above the pre-injury flow. The flow begins to decrease and after one hour remains below the control flow for the remainder of the experiment.

The animals which received hypertonic saline at 5 minutes following injury had a greater increase in flow when compared to animals in the untreated group during the same time interval. The maximum flow in the treated group occurred approximately 5 minutes from the start of hypertonic saline administration. While the duration of hyperemia was not different between the treated and untreated groups, the magnitude of hyperemia was significantly greater in the hypertonic saline-treated group.

Hypertonic saline and nitroprusside show different effects on the spinal cord blood flow depending on the state of the tissue (Fig. 3). When nitroprusside was

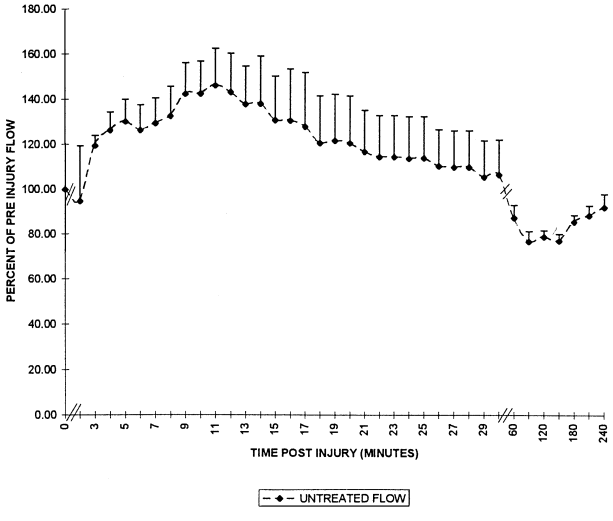

Fig. 1. Flow changes following spinal cord injury in untreated animals. Flow is represented as percent of the pre injury flow. Time 0 represent mean ± standard error. $n = 5$

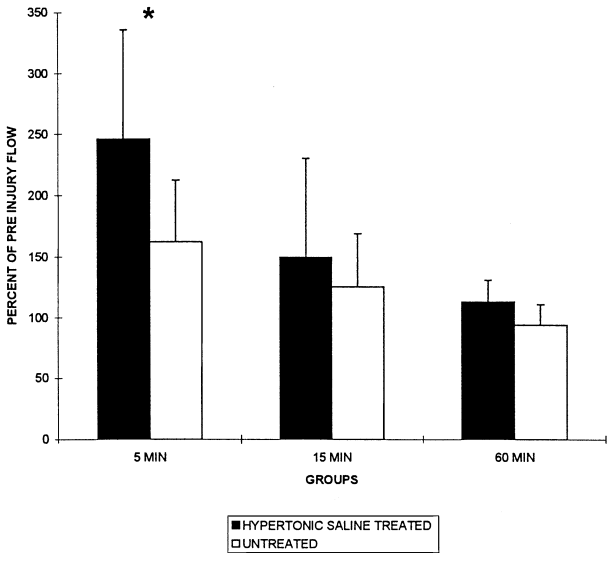

Fig. 2. The solid bar represents the maximum flow as percent of pre injury flow in animals treated with 7.5% hypertonic saline at the indicated time. The open bar represents the maximum flow in the untreated group as percent of pre injury flow.

*$P < 0.05$ the maximum flow in the group treated at 5 minutes post injury is significantly greater than the maximum flow in the untreated group during the same time interval. Values represent mean $\pm$ standard deviation. n = 5. See Fig. 2

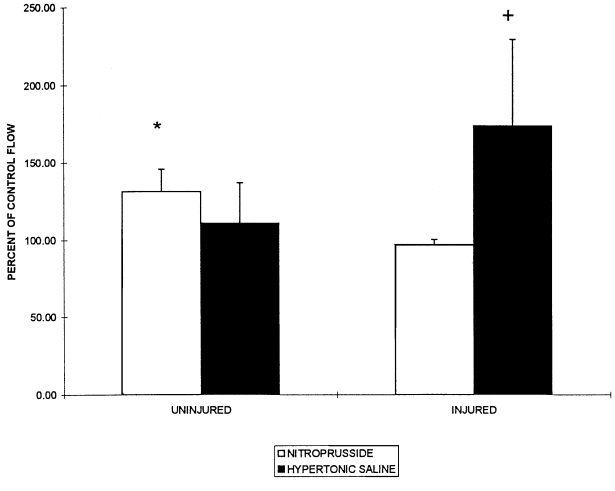

Fig. 3. Maximum change in spinal cord blood flow following the administration of nitroprusside (open bar) and hypertonic saline (solid bar) represented as percent of the control flow. The control flow is the flow immediately before nitroprusside or hypertonic saline administration.

*$P < 0.04$ significant increase in flow following nitroprusside administration.

+$P < 0.05$ significant increase in spinal cord blood flow in injured animals following hypertonic saline administration. Values represent mean $\pm$ standard deviation. n = 5

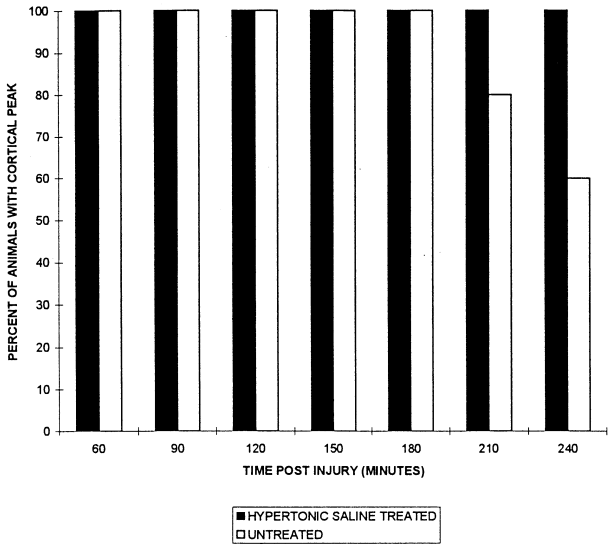

Fig. 4. The percent of animals with somatosensory evoked potentials at the indicated time periods post injury. The solid bar represents the hypertonic saline treated groups and the open bar represents the untreated group. n = 5

administered to uninjured animals, flow was significantly increased by 31% ($p < 0.05$). However, when nitroprusside was applied 10 minutes following spinal cord injury, there was no significant change in the spinal cord blood flow. Even when higher doses of nitroprusside were used which caused a decrease in mean arterial pressure, there was still no change in flow. However, when hypertonic saline was administered to injured animals following nitroprusside application, flow was significantly increased by 74% ($p < 0.05$), while there was no significant change in flow when hypertonic saline was administered to uninjured animals.

Somatosensory evoked potentials were measured and compared before and after the laminectomy in order to ensure there was no change in the quality of the cortical peak due to surgery. The cortical peak of the SSEP in the sham group was measured before and after hypertonic saline administration. There was no change in the cortical peak of the SSEP after hypertonic saline administration in the sham animals which suggests that hypertonic saline does not change the magnitude of the cortical peak in uninjured animals.

The cortical peaks were absent during the injury period in all groups and the peaks of all animals (treated and untreated) returned following injury. The cortical peak in animals treated with hypertonic saline (Fig. 4) were maintained for four hours following injury while the cortical peak in the untreated animals began to disappear three hours post injury. The mean

Table 1.

Mean Arterial Blood Pressure										
Time of Hypertonic Saline Administration										
	Untreated		5 Minutes		15 Minutes		30 Minutes		60 Minutes	
	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
con	135.00	13.69	145.00	11.18	138.00	16.05	155.00	20.92	131.00	27.02
d5	106.00	23.82	109.00	22.19	98.00	23.61	110.00	13.69	77.00	25.15
d10	52.00	25.64	62.00	19.56	59.00	20.43	64.00	10.84	81.00	43.36
5	109.00	52.96	115.00	10.00	121.00	11.94	144.00	13.87	123.00	28.20
15	130.00	27.39	141.00	14.75	145.00	13.23	152.00	18.23	141.00	26.79
30	128.00	21.97	141.00	14.75	145.00	13.23	152.00	18.23	139.00	26.08
60	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	137.00	29.92
90	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	140.00	23.45
120	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	142.00	24.90
150	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	142.00	24.90
180	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	142.00	24.90
210	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	142.00	24.90
240	123.00	30.94	140.00	13.69	145.00	13.23	154.00	18.51	142.00	24.90

arterial blood pressure for the animals in each group at various time periods is represented in Table 1. There was no statistically significant difference in the pressure at any time point between groups.

Discussion

Manipulation of factors mediating secondary injury after spinal cord trauma represents an opportunity to minimize overall damage to the spinal cord. A number of factors could contribute to this secondary exacerbation of spinal cord injury. Included among these factors are free radical production, enzymatic changes, stimulation of inflammatory mediators, activation of platelets and leukocytes, vasospasm, endothelial cell swelling and endothelial dysfunction [1, 2, 4, 9, 14, 17, 18, 21, 25, 30]. All of these changes could contribute to an increase in local vascular resistance and a reduction in spinal cord blood flow following injury.

Evidence that severe spinal cord injury leads to a reduction in spinal cord perfusion has been provided by a number of investigators. It has been suggested that the magnitude, and even the direction of the flow changes are related to the severity of injury [9]. Hall *et al.* (1986) have suggested that there is a tendency for white matter blood flow to initially increase following subparalyzing injuries [9]. This may explain the results obtained in the current investigation where we found an initial reactive hyperemia following the removal of compression. Flow then returned to control values by 60 minutes and then remained below control values for the remainder of the experimental period. Hypoperfusion after the initial hyperemia would appear to be the result of the secondary changes that increase vascular resistance following injury.

There has been considerable interest in the development of methods to maintain spinal cord blood flow following injury. Young *et al.* (1982) demonstrated the beneficial effects of high doses (>30 mg/kg) of methylprednisolone [29].

They postulated that at high doses, the primary effect of the steroid was to inhibit free radical damage. This in turn would prevent increases in spinal cord vascular resistance and tissue hypoperfusion. Several years later, Hall *et al.* (1989, 1992) provided additional evidence of the importance of free radical inhibition [8, 10]. These investigators found that the administration of 21-aminosteroid prevented lipid peroxidation and the associated increase in spinal cord vascular resistance.

The hypothesis that pharmacologic agents which help to maintain post-traumatic spinal cord blood flow may contribute to preservation of cord function stimulated our laboratory to investigate the potential usefulness of hypertonic saline administration following spinal cord injury. The administration of hypertonic saline during hemorrhagic shock causes a transient increase in cardiac output, a decrease in peripheral and pulmonary vascular resistance and an increase in mean arterial pressure [13, 15]. These effects are thought to be accomplished, at least in part, through rapid mobilization of extravascular fluid vol-

ume and a direct positive inotropic effect [13]. Several studies have found that when sued as a resuscitative agent, hypertonic saline had beneficial effects on intracranial pressure and cerebral blood flow [3, 9, 22, 23]. In studies where animals were subjected to hemorrhage or a combination hemorrhage and head injury, animals which received hypertonic saline demonstrated a decreased intracranial pressure and increased regional cerebral blood flow compared to animals which were resuscitated with normal saline [3, 19, 22, 23]. Hypertonic saline has also been shown to be a potent vasodilator with preferential effects on specific vascular beds [7, 26].

Our laboratory (1994) was the first to evaluate the effect of hypertonic saline administration on blood flow changes following spinal cord injury [30]. In these studies, hypertonic saline was administered one minute after spinal cord injury and spinal cord blood flow and somatosensory evoked potentials were followed for a period of one hour. Hypertonic saline administration was found to have a significant impact, not only on spinal cord blood flow, but also on preserving somatosensory evoked potentials. The magnitude of reactive hyperemia was increased in the animals receiving hypertonic saline. Somatosensory evoked potentials were also better preserved in animals treated with hypertonic saline. It was concluded from a comparison of the effects of equivalent volume expansion with isotonic saline that the changes in spinal cord blood flow were not due to systemic hemodynamic effects, but rather to local vascular changes within the spinal cord.

There are a number of mechanisms through which hypertonic saline administration could contribute to decreasing vascular resistance within the spinal cord. As already mentioned, hypertonic saline may cause an osmotically induced relaxation of vascular smooth muscle. Post-traumatic swelling of endothelial cells which may result in reduction of spinal cord perfusion has been observed by Nemecek [14]. Mazzoni *et al.* (1989, 1990) have provided evidence that hypertonic saline administration can reduce endothelial swelling in skeletal muscle [11, 12]. It is also possible that hypertonic saline could have a number of antiinflammatory effects that could influence local vascular resistance. It has been shown in several studies that animals resuscitated following hemorrhage with hypertonic saline exhibited decreased leukocyte adhesion and rolling in skin blood vessels [16, 20].

Downregulation of leukocyte and endothelial activation following injury could attenuate secondary inflammatory changes that would lead to a reduction in tissue perfusion.

One of the limitations of the study of Young *et al.* (1994) was that hypertonic saline was administered within a minute after injury [30]. If the beneficial effects of spinal cord administration demonstrated by this study could only be obtained when hypertonic saline was administered within a few minutes of spinal cord injury the clinical applicability of this treatment would of course be quite limited. The purpose of the current study was to evaluate the effects of hypertonic saline administration at various time periods after injury and to try and shed further light on how alterations in spinal cord vascular resistance might be effected.

An interesting result of this study was the finding that the effect of hypertonic saline administration on spinal cord blood flow was directly related to the time of administration after injury. The magnitude of hyperemia was significantly less when administered 15 and 60 minutes after injury. To determine whether the time dependency of this effect was related to the ability of the vascular smooth muscle to relax at various time periods after injury we compared the effects of hypertonic saline administration with the effects of exposure of the vessels to sodium nitroprusside. Interestingly the effect of nitroprusside superfusion and hypertonic saline administration differed significantly in relationship to the pathophysiologic state of tissue. When the uninjured spinal cord was exposed to nitroprusside, there was a significant increase in blood flow; however, hypertonic saline administration to uninjured animals caused no significant change in spinal cord blood flow.

In contrast to these results, administration of nitroprusside immediately after injury had no effect on spinal cord blood flow while hypertonic saline administration at this time had its greatest effect. These results indicate that the effect of hypertonic saline administration administration on local blood flow may be directly related to the pathophysiologic condition of the blood vessels. It appears that hypertonic saline has relatively little effect on spinal cord vascular resistance under normal conditions, but does have a significant effect under pathologic conditions. This could have important implications for the ability of hypertonic saline to selectively increase blood flow in regions of compromised perfusion.

A somewhat surprising finding was the result that all animals receiving hypertonic saline, including those treated at 15 and 60 minutes after injury maintained somatosensory evoked potentials throughout the ex-

perimental period while only 60% of the untreated animals had evoked potentials for four hours. Somatosensory evoked potentials in the hypertonic saline treated animals appeared to be better preserved even though the duration of hyperemia following hypertonic saline administration lasted less than 10 minutes and the effect of hypertonic saline on blood flow was greatly attenuated at later time periods of administration. These results may indicate that the protective effect of hypertonic saline on spinal cord function could be the consequence of changes that occur in addition to alteration in blood flow. Although the results obtained in this study do not allow for definitive conclusions, they could be related to the finding that one of the effects of hypertonic saline administration may be downregulation of the inflammatory response. We have previously been able to demonstrate in our spinal cord injury model and a skin model chamber preparation that hypertonic saline administration decreases leukocyte rolling and sticking to both arterial and venous vessels [24].

Leukocyte rolling and sticking is an essential component for the participation of the circulating white cells in the inflammatory response. Attenuation of these functions could decrease cellular damage due to the production of free radicals, proteases and other cytotoxic mediators by the white cells, endothelial cells and platelets after spinal cord injury.

We are currently conducting behavioral studies to determine the effects of hypertonic saline administration in a chronic model of spinal cord injury. Ultimately, the benefits of hypertonic solutions in spinal cord injury will depend on preservation and improvement of neurologic function.

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Comments

Obviously, the present experiments require some comments. A major point, blood flow depression from injury, did not occur rendering administration of hypertonic saline questionable as a procedure to improve blood flow. With regard to the quoted literature on spinal cord injury and blood flow the authors should provide respective findings of the other laboratories in more details for a comparison and discussion with their own data. Potential contradictions then might be discussed with regard to differences in the experimental model or to the procedure of flow measurement by Laser Doppler fluxmetry. This notwithstanding, administration of hypertonic saline induced at least for 5 min a marked flow increase up to nearly 250% of control, falling then to ca. 150% at 15 min or 110–120% at 60 min, with the latter flow level not being significant vs. control. The question here may be asked, whether this enhancement by hypertonic NaCl of the hyperemia, already spontaneously evolving from injury, might actually not support secondary tissue damage from trauma, e.g. by an increase in blood cord barrier disruption and spread of edema.

Further, the inverse flow response of the cord tissue to NNP vs. hypertonic NaCl is intriguing, raising a variety of questions. One is why hypertonic saline is raising blood flow only in damaged tissue while not in normal cord, or why is the flow response to NNP just the opposite of that induced by hypertonic saline?

The most important point is that the present findings do not provide a clear answer to the underlying question, whether hypertonic solution is beneficial or not, as secondary ischemia was not induced by the spinal cord lesion. On the other hand, it might be admitted that hypertonic saline had some therapeutic properties with regard to the seemingly better maintenance of evoked potentials, although the presentation of data here is quite deficient.

A. Baethmann

In a previous publication the senior author showed that hypertonic saline administered following spinal cord injury within a minute improved local blood flow and helped to maintain somatosennsory evoked potentials. In this well-planned study the authors investigated whether the spinal beneficial effects of administration of hypertonic saline can also be achieved with a more delayed timing/start of the treatment. It appeared that hypertonic saline had relatively little effect on the spinal cord circulation under normal conditions but had a significant effect following cord compression. The authors hypotethise that hypertonic saline is capable of selectively increasing spinal cord blood flow in regions of compromised circulation, and it has additional protective effects which are independent of alteration of blood flow.

The question to be elucidated has remained whether the same improvement can be achieved in human spinal cord injury.

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