New Developments in the Pharmacologic Management of Posttraumatic Oedema

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A major risk factor contributing to increased mortality and morbidity following traumatic brain injury (TBI) is oedema formation. Recent efforts by our laboratory, and others, have concentrated on establishing the mechanisms associated with oedema formation following brain injury, and developing appropriate pharmacologic interventional therapies. Our own studies to date have shown that neurogenic inflammation is a major contributor to brain oedema formation. Attenuation of the neurogenic inflammation, either by preventing release of the neuropeptides or blocking substance P receptor binding, profoundly inhibited these events. We propose that pharmacologic intervention targeting neurogenic inflammation may be a promising strategy for the management of posttraumatic oedema.

Introduction

Traumatic brain injury (TBI) is the biggest killer of individuals under 44 years of age in industrialized countries. In younger victims of TBI, almost 50% of death and disability has been reported to be associated with uncontrolled brain swelling (Feickert et al., 1999), while in all age groups combined, 50% of all deaths following severe brain injury can be accounted for by this factor (Marmarou, 2003). It therefore comes as no surprise that reduction of brain oedema and swelling is one of the major objectives in the clinical management of TBI.

Approaches to clinical oedema management are widely varied and include hyperventilation, cranial decompression, osmotic agents, and pharmacological interventions such as barbiturates and steroids (Reilly, 1997). The success of these approaches, and in particular the pharmaco-

logical interventions, has been limited largely due to the fact that they do not address the mechanisms associated with oedema formation. In part, this has been because the mechanisms have remained obscure. However, over the past few years, significant progress has been made in understanding oedema formation, including the contributions of both vasogenic and cytotoxic oedema to posttraumatic brain swelling.

Oedema after TBI

A number of studies in different models have now demonstrated that TBI is followed by two phases of oedema (Marmarou, 2003). The first is a transient vasogenic phase that increases the extracellular water concentration. The blood brain barrier is permeable during this phase. Thereafter, there is an intracellular accumulation of water that persists for several days. In the absence of any blood brain barrier opening, the second phase of oedema is thought to largely represent cytotoxic oedema. Significantly, Marmarou and colleagues (Beaumont et al., 2000) have reported that the initial vasogenic oedema is permissive for the formation of the later cytotoxic phase. This raises the possibility that inhibiting the initial vasogenic component of posttraumatic brain oedema may also attenuate the later formation of cytotoxic oedema.

Vasogenic oedema

Vasogenic oedema is characterised by disruption of the blood brain barrier, and this increased permeability is central to oedema development. A variety of factors that cause disruption have been identified including bradykinin, histamine, arachidonic acid, leukotrienes, interleukins, and tumour necrosis factor, amongst others (Abbott, 2000). Many of these factors are inflammatory mediators, supporting the concept that tissue oedema constitutes the major marker of an inflammatory process. One inflammatory process that has received little attention in the CNS, but has long been recognised as a major factor in peripheral tissue oedema, is neurogenic inflammation (Campos and Calixto, 2000).

Neurogenic inflammation is a neurally elicited reaction that has typical characteristics of an inflammatory reaction including vasodilation, protein extravasation and tissue swelling. Studies in peripheral tissue have demonstrated that neurogenic inflammation is the result of the stimulation of C-fibres, which causes the release of neuropeptides (Woie et al., 1993). Although a number of neuropeptides have been implicated in this process, it is generally accepted that substance P (SP) is primarily associated with an increase in microvascular permeability leading to oedema formation (Campos and Calixto, 2000). Virtually all blood vessels of the body are surrounded by sensory nerve fibres that contain these neuropeptides. Cerebral arteries, in particular, appear to receive a dense supply of these

neurones, and it is therefore consistent that these neurones have a role as mediators of the inflammatory process.

Neurogenic inflammation after TBI

Our recent studies have concentrated on characterising the role of neurogenic inflammation after TBI. We have shown that prior depletion of neuropeptides using the vanilloid agonist, capsaicin, profoundly inhibits the development of vasogenic oedema formation after TBI (Nimmo et al., 2004). There was also an attenuation of oedema formation at later time points, consistent with the concept that vasogenic oedema is permissive for later cytotoxic oedema. Since substance P has been identified as the neuropeptide that is primarily responsible for oedema formation following peripheral tissue injury (Campos and Calixto, 2000), and the neurokinin-1 (NK_1) receptor has been identified as being critical to this development, we subsequently examined whether administration of an NK_1 antagonist after TBI could attenuate oedema formation. When the NK_1 antagonist, n-acetyl-tryptophan, was administered 30 min after the traumatic event, there was an attenuation of blood brain barrier permeability and a significant reduction in oedema formation. This reduction in oedema formation was accompanied by a significant improvement in functional outcome. Our results are consistent with the hypothesis that neurogenic inflammation plays an integral role in the increased permeability of the blood brain barrier after TBI and the associated development of vasogenic oedema.

Mechanisms

Figure 1 illustrates the mechanisms whereby administration of an NK_1 antagonist can potentially attenuate disruption of the blood brain barrier and inhibit vasogenic oedema formation after TBI. TBI induces the release of neuropeptides including substance P, calcitonin gene related peptide (CGRP), neurokinin A and neurokinin B, amongst others. This release can be stimulated by a number of factors including acidosis or vanilloid agonists. Once released, neurokinin A and B as well as substance P can bind to neurokinin receptors on the target cell. While substance P can bind to all three receptors, it has a much higher affinity for the NK_1 receptor. Activation of the neurokinin receptors stimulates the formation of eicosanoids via the cyclo-oxygenase pathway (Hartung et al., 1988), nitric oxide (Sterner-Kock et al., 1999) and the kinin-kallikrein pathway (Campos and Calixto, 2000), all of which are inflammatory mediators that can disrupt the blood brain barrier. The release of bradykinin can also activate further neuropeptide release by binding to bradykinin receptors on the neurone (Campos and Calixto, 2000). Substance P can also stimulate the production of serotonin and histamine by mast cells, with the

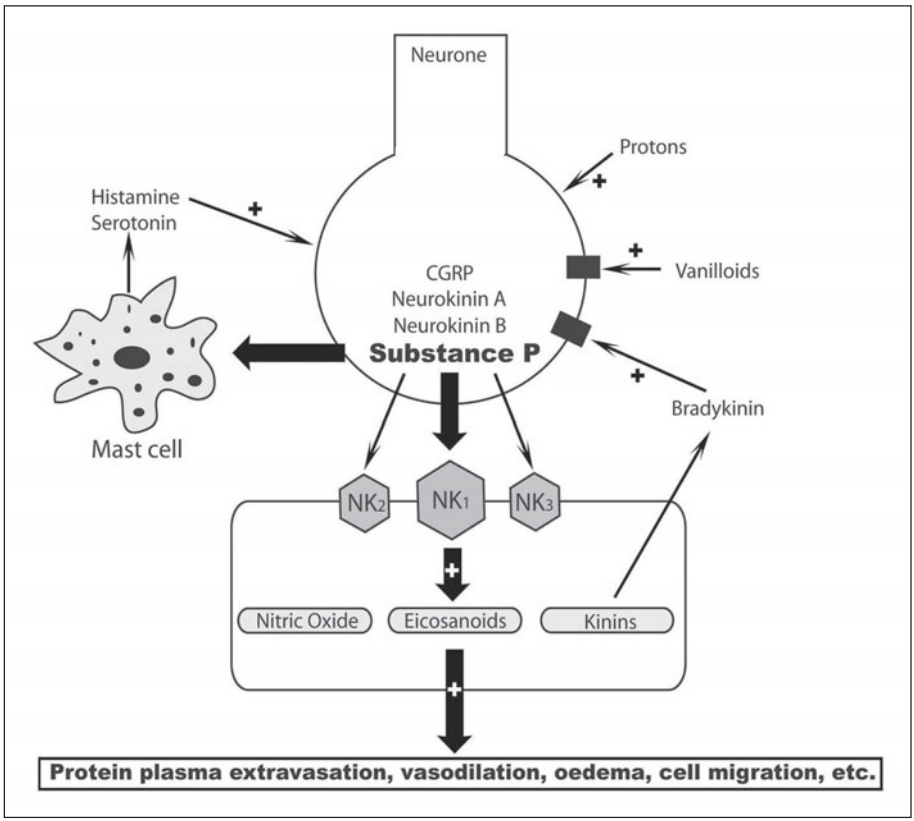

Figure 1. *Mechanisms associated with the development of neurogenic inflammation after TBI.*

latter also activating further release of the neuropeptides. Finally, it should be noted that CGRP has been shown to potentiate the actions of substance P, although its co-release is not a mandatory requirement for substance P induced neurogenic inflammation (Brain et al., 1995).

Other pharmacological interventions

A number of compounds have been shown to inhibit oedema formation following TBI, although the mechanisms associated with this effect have been largely unknown. Having identified the critical role that neurogenic inflammation may play in vasogenic oedema formation, some of the actions of these successful therapies may be rationalized in terms of actions on neurogenic inflammation. For example, bradykinin B2 receptor antagonists have been shown to reduce oedema formation following ex-

perimental TBI (Stover et al., 2000). This action may be mediated through effects on neurogenic inflammation since bradykinin B2 receptor antagonists have been reported to reduce neurogenic inflammation (Linardi et al., 2000). Similarly, a number of studies with progesterone and its metabolites have shown that the neurosteroid attenuates oedema formation after TBI (Wright et al., 2001). What is significant is that neurosteroids block neurogenic inflammation, particularly progesterone and allopregnanolone (Limmroth et al., 1996). Similarly, cannabinoids have been shown to reduce oedema formation following TBI (McCarron et al., 2003). However, cannabinoids are known agonists of the vanilloid receptor (Grotenhermen, 2004), and both agonists and antagonists of the vanilloid receptor have been found capable of preventing the development of neurogenic inflammation or even abolishing an ongoing inflammatory process (Linardi et al., 2000).

Conclusion

We have identified that neurogenic inflammation, and particularly substance P, plays a critical role in the development of oedema formation following TBI. Inhibition of neuropeptide release, or inhibition of the NK_1 receptor, significantly attenuates the posttraumatic opening of the blood brain barrier and subsequent development of vasogenic oedema. A number of pharmacological agents that have previously been shown to attenuate posttraumatic oedema have an interaction with the pathways associated with neurogenic inflammation, and may thus mediate their effects via modulation of this pathway.

References

ABBOTT NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. Cell. Mol. Neurobiol. 20:131-147, 2000.

BEAUMONT A, MARMAROU A, HAYASAKI K, et al. (2000). The permissive nature of blood brain barrier (BBB) opening in edema formation following traumatic brain injury. Acta Neurochir. Suppl. 76:125-129, 2000.

BRAIN SD, NEWBOLD P, KAJEKAR R. Modulation of the release and activity of neuropeptides in the microcirculation. Can. J. Physiol. Pharmacol. 73:995-998, 1995.

CAMPOS MM, CALIXTO JB. Neurokinin mediation of edema and inflammation. Neuropeptides 34:314-322, 2000.

FEICKERT HJ, DROMMER S, HEYER R. Severe head injury in children: impact of risk factors. J. Trauma 47:33-38, 1999.

GROTENHERMEN F. Pharmacology of cannabinoids. Neuro. Endocrinol. Lett. 25:14-23, 2004.

HARTUNG HP, HEININGER K, SCHAFER B, et al. Substance P and astrocytes: stimulation of the cyclooxygenase pathway of arachidonic acid metabolism. FASEB J. 2:48-51, 1988.

LIMMROTH V, LEE WS, MOSKOWITZ MA. GABAA-receptor-mediated ef-

fects of progesterone, its ring-A-reduced metabolites and synthetic neuroactive steroids on neurogenic oedema in the rat meninges. Br. J. Pharmacol. 117:99-104, 1996.

LINARDI A, COSTA SK, DA SILVA GR, et al. Involvement of kinins, mast cells and sensory neurons in the plasma exudation and paw oedema induced by staphylococcal enterotoxin B in the mouse. Eur. J. Pharmacol. 399:235-242, 2000.

MARMAROU A. Pathophysiology of traumatic brain edema: current concepts. Acta Neurochir. Suppl. 86:7-10, 2003.

MCCARRON RM, SHOHAMI E, PANIKASHVILI D, et al. Antioxidant properties of the vasoactive endocannabinoid, 2-arachidonoyl glycerol (2-AG). Acta Neurochir. Suppl. 86:271-275, 2003.

NIMMO AJ, CERNAK I, HEATH DL, et al. Neurogenic inflammation is associated with development of edema and functional deficits following traumatic brain injury in rats. Neuropeptides 38:40-47, 2004.

REILLY PL. Management of intracranial pressure and cerebral perfusion, In: Head Injury: Pathophysiology and Management of Severe Closed Head Injury (Reilly PL, Bullock R, eds), pp 385-406. Chapman and Hall, Sydney, 1997.

STERNER-KOCK A, BRAUN RK, VAN DER VLIET A, et al. Substance P primes the formation of hydrogen peroxide and nitric oxide in human neutrophils. J. Leukoc. Biol. 65:834-840, 1999.

STOVER JF, DOHSE NK, UNTERBERG AW. Significant reduction in brain swelling by administration of nonpeptide kinin B2 receptor antagonist LF 16-0687Ms after controlled cortical impact injury in rats. J. Neurosurg. 92:853-859, 2000.

WOIE K, KOLLER M, HEYERAAS KJ, et al. Neurogenic inflammation in rat trachea is accompanied by increased negativity of interstitial fluid pressure. Circ. Research 73:839-845, 1993.

WRIGHT DW, BAUER ME, HOFFMAN SW, et al. Serum progesterone levels correlate with decreased cerebral edema after traumatic brain injury in male rats. J. Neurotrauma 18:901-909, 2001.