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Substance P: A Novel Target in the Treatment of Cerebral Oedema and Elevated Intracranial Pressure Following Traumatic Brain Injury

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1. Introduction

Traumatic brain injury (TBI) is the biggest killer of individuals under the age of 44 years [1], affecting over 5 million individuals worldwide each year. Many individuals are left with permanent neurological deficits caused by a number of complex biochemical cascades, referred to as secondary injury, that are initiated by the traumatic event and evolve over the hours to days thereafter. Secondary injury encompasses a wide variety of injury factors including excitotoxicity, loss of ion homeostasis, oxidative stress, inflammation, apoptosis, increased vascular permeability and cerebral oedema, amongst many others [2-3], and has been well documented to exacerbate injury and worsen outcome following trauma. Nevertheless, the delayed fashion in which the injury progresses provides a window of opportunity for therapeutic intervention to potentially halt secondary injury, reduce neuronal loss and improve outcome. As such, countless studies have now focused on characterising the secondary injury that occurs following trauma in order to develop therapies to reduce or ameliorate such pathways [4].

However, the findings of neuroprotective studies have to date produced unfavourable outcomes in clinical trials [2]. Although the reasons for such failures are multifactorial, it is apparent that targeting only a single injury factor is of limited benefit when numerous cascades contribute to the resultant injury. Alternatively, if a target is identified that modulates many aspects of secondary injury then this may produce favourable results [5]. Of the secondary injury pathways, disruption to the blood-brain barrier (BBB) and subsequent development of cerebral oedema are of particular concern due to the potential effect on intracranial pressure (ICP) dynamics [6]. In this review, we highlight recent data delineating a potentially crucial

role for the neuropeptide substance P (SP) in the pathogenesis of cerebral oedema formation and the development of elevated ICP following TBI, and the multi-potential nature of SP antagonists as a therapeutic intervention.

2. Blood-brain barrier disruption

Under normal conditions the BBB provides a selectively permeable barrier between the vasculature and the brain that regulates the entry of blood-borne substances, thereby maintaining an optimal environment within the brain [7]. It is comprised of a complex network of cells that make up the cerebral capillaries and post-capillary venules, resting on the basal lamina [8]. The gate function of the BBB is provided by the tight and adherin junctions, composed of a complex network of transmembrane and cytosolic proteins [7]. The BBB functions to ensure a constant supply of nutrients, preserves ion homeostasis within the brain microenvironment and protect against noxious chemicals, variations in blood composition and breakdown of concentration gradients.

After trauma, alterations in BBB permeability have been well documented [9-11], with the temporal profile of BBB disruption largely dependent upon the type of injury. Specifically, early increases in BBB permeability are observed following models of diffuse TBI [12], whilst a biphasic opening of the BBB has been reported in more focal injuries [13]. Nevertheless, BBB dysfunction is permissive to the generation of cerebral oedema, specifically of the vasogenic type. In this type of cerebral oedema extravasation of plasma proteins occurs followed by a net movement of fluid from the vascular compartment into the brain parenchyma, leading to a disruption of both fluid and ionic homeostasis. Given the increase in the volume of the brain tissue under these circumstances, vasogenic oedema has the potential to markedly alter intracranial pressure dynamics [6] and negatively influence patient outcomes [13]. In addition, the loss of barrier integrity following acute injury to the brain allows peripheral immune cells to cross the barrier and further contribute to and exacerbate in the inflammatory processes within the brain [14].

3. Development of cerebral oedema

Of the secondary injury factors, cerebral oedema is of particular importance in terms of patient morbidity and mortality [15]. Indeed, cerebral oedema is a leading cause of death following TBI and a predictor of poor outcome in those individuals that survive. Specifically, it accounts for as much as half of all morbidity and mortality [15-16], largely because it increases intracranial pressure (ICP), resulting in reduced cerebral blood flow, initiation or exacerbation of an ischaemic state, deformation and herniation of brain tissue and a substantial increase in morbidity and mortality [17]. As such, brain oedema with increased ICP is widely recognised as a major clinical management target [18]. Despite this, there is currently no effective pharmacological treatment that reduces the considerable mortality and morbidity associated with

cerebral oedema [15, 17]. Indeed, conventional treatments targeting cerebral oedema and elevated ICP, using for example hyperventilation, mannitol, diuretics, or barbituates [17], do not address the mechanisms associated with oedema formation but rather focus on the net result. Although these agents and interventions have, under ideal conditions, been shown to reduce ICP, their capacity to produce sustained decreases in ICP is inadequate. Furthermore, their effectiveness is limited as once cerebral oedema produces evidence of mass effect with midline shift on imaging, fatality rates become high, irrespective of treatment.

Decompressive craniectomy is a surgical procedure in which a large flap of bone overlying the swollen brain is removed, creating space to accommodate the increased volume associated with cerebral oedema [17]. This is currently one of the most powerful tools that clinicians have to combat elevated ICP, although it has been shown to improve survival in some studies, whilst associated with an increase in moderate to severe disability in others [19, 20], thereby emphasising the need for further clinical studies to clearly determine the effect of decompressive surgery following TBI. Furthermore, as decompressive craniectomy is a major operation, it is complicated in the gravely ill and the efficacy is markedly decreased in patients over 60 years of age; thus many patients are ineligible for the surgery [17]. Overall, such treatments and interventions have proven to be largely ineffective in combating cerebral oedema, mainly because they do not actually address the specific mechanisms that produce swelling of brain tissue. Recent studies in experimental TBI have identified that release of the neuropeptide substance P (SP) is a feature of acute injury to the brain and have revealed a crucial role for SP in the increases in vascular permeability and brain water content which are observed following TBI. As such, they may represent a novel pharmacological target for the treatment of oedema and increased ICP.

4. Substance P

SP is an 11 amino acid peptide and member of the tachykinin peptide family, which also includes neurokinin A (NKA), neurokinin B (NKB) and neuropeptide γ , amongst others [21]. Originally identified by von Euler and Gaddum in the 1930's for its potent smooth muscle and hypotensive properties [21], it is now known that SP is released from primary afferent nerves in both the peripheral and central nervous systems where it functions as a neurotransmitter [22]. SP is also released from non-neuronal cells such as endothelial and inflammatory cells [23]. Specifically, within the nervous system, SP is localised in capsaicin-sensitive neurons and is released in response to calcium-dependent depolarisation induced by various stimuli including electrical stimulation, pH changes and ligand-receptor binding [24]. Following release, SP can exert direct post-synaptic actions as a neurotransmitter, or modulate other non-neuronal targets [25], via binding to tachykinin NK receptors. The NK receptors are members of the rhodopsin family of 7-transmembrane domain G-protein coupled receptors. To date, 3 mammalian tachykinin receptors have been identified, namely the NK1, NK2 and NK3 receptors [22]. There is some cross-reactivity amongst the receptors, with each tachykinin able to bind all receptors types depending on neuropeptide concentration and receptor availability [22]. However, under normal conditions SP has the highest affinity for the NK1 receptor, NKA

for the NK2 receptor and NKB for the NK3 receptor. Furthermore, the predominance of the NK1 receptor in the human adult brain [26] makes SP the main tachykinin of interest in the pathophysiology of CNS injury. Transduction of the SP signal through the NK1 receptor occurs via G protein signalling and the secondary messenger cAMP, ultimately leading to the regulation of ion channels, enzyme activity and alterations in gene expression [25].

5. Neurogenic inflammation

The release of neuropeptides, including SP and calcitonin gene-related peptide (CGRP), leads to the development of neurogenic inflammation, a neurally elicited, painful local inflammatory response that is characterised by vasodilation, increased vascular permeability, mast cell degranulation and protein extravasation [27]. Such changes in blood vessel size and permeability lead to the development of tissue swelling [27]. In addition, there are also other responses that are specific to individual tissues, including, for example, smooth muscle contraction/relaxation in the bladder and bronchoconstriction in the airways, amongst others. Although other neuropeptides such as CGRP are involved, SP is considered to be the most potent initiator of neurogenic inflammation. Nevertheless, CGRP can potentiate the effects of SP by increasing the expression of the NK1 tachykinin receptor and enhancing the bioavailability of SP by competing with SP for catabolism by endopeptidases [28]. Indeed, neurogenic inflammation leads to an increase in the PPT and NK1 receptor mRNA transcript, which encodes SP and its receptor.

5.1. Peripheral nervous system

It has been well documented that neurogenic inflammation occurs in peripheral tissues such as the oral, nasal, facial and ocular tissue, with release of SP known to initiate increased microvascular permeability and tissue swelling [29]. Indeed, SP, NKA or NKB injected into the paws of rats leads to a profound increase in paw swelling with a similar response observed following the administration of exogenous NK1, NK2 or NK3 agonists [30]. Furthermore, administration of NK1, NK2 or NK3 tachykinin receptor antagonists inhibits such oedema formation in a dose-dependent manner. These findings confirm the involvement of SP, NKA and NKB in the genesis of neurogenic inflammation and tissue swelling, and clearly implicates all three tachykinin ligand-receptor pairs in the observed neurogenic inflammatory responses. Nonetheless, the predominant role of SP in neurogenic inflammation has been confirmed in NK1 tachykinin receptor negative mice [31].

5.2. Central nervous system

The involvement of classical inflammation in the evolution of injury following TBI has been known for some time, however the concept of neurogenic inflammation in the brain has until recently remained unexplored. Originally described in peripheral tissues, it is now known that neurogenic inflammation occurs in the brain following injury [12, 32-38]. In stroke,

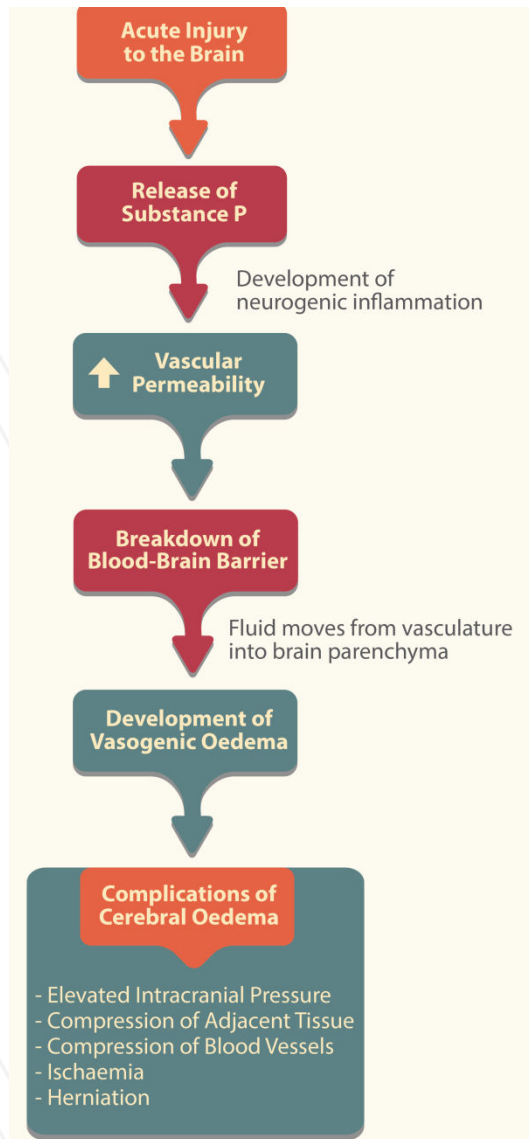


Figure 1. Release of substance P and the development of neurogenic inflammation following acute brain injury.

Stumm and colleagues (2002) proposed that activation of NK1 tachykinin receptors on vascular endothelium may contribute to cerebral oedema [39]. Indeed, chemical or electrical stimulation of the dura mater or treatment with capsaicin produces a neurogenic inflammatory response in the dura mater but was not observed in the pia mater or within the brain parenchyma itself [40]. Furthermore, administration of SP produced a marked increase in plasma extravasation

within the dura mater of rats, an effect that was blocked by administration of an NK1 tachykinin receptor antagonist [41]. Such studies confirm the presence of neurogenic inflammation within the brain and the involvement of SP in changes in vascular permeability in the setting of injury. More recently, neurogenic inflammation in the brain has been widely characterised in a variety of acute injuries to the central nervous system (Figure 1) in animal models, including trauma [12, 32-33, 37, 42], stroke [34-36, 38] and spinal cord injury [43]. Furthermore, activation of the multimodal transient receptor potential vanilloid 1 (TRPV1) receptor initiates neurogenic inflammation [44] and is associated with increased BBB permeability, an effect abolished by the TRPV1 antagonist capsazepine [45]. Given that TRPV1 receptors are co-localised with both SP and CGRP suggests that it plays a role in BBB dysfunction following acute injury as a facilitator of neurogenic inflammation.

6. Substance P in traumatic brain injury

Our studies have shown that SP release is a ubiquitous feature of acute injury to the brain and is associated with marked increases in BBB permeability, cerebral oedema and functional deficits [12]. Specifically, an increase in SP was observed in brain following diffuse TBI that was particularly profound in the perivascular tissue. Such increases in SP immunoreactivity were observed at 5h and shown to persist to at least 24h following trauma in rats [12]. PCR studies later confirmed that SP levels mRNA remained elevated until 3 days post-trauma [46]. Serum levels of SP were also shown to be elevated following trauma, with significant increases observed at 30 mins [12], although levels declined quite rapidly after this time this most likely reflecting the rapid proteolysis of SP within the serum by non-specific proteases. Interestingly, when SP breakdown is inhibited through the administration of an angiotensin-converting enzyme inhibitor, an increase in SP immunoreactivity is observed with an exacerbation of injury and neurological dysfunction [47]. Taken together, these studies confirm that SP release is a feature of acute injury to the brain.

Increased SP levels following trauma have been associated with changes in cerebral vascular permeability and cerebral oedema. Specifically, in rodent TBI increased SP immunoreactivity within injured brain tissue was shown to co-localise with exogenously administered Evan's Blue dye, a marker of BBB breakdown [12]. Such alterations in vascular permeability were also associated with the development of cerebral oedema of the vasogenic type [12]. Persistent functional deficits, both motor and cognitive, were also observed in the setting of neurogenic inflammation following TBI [12, 32]. More recently, a role for neurogenic inflammation in BBB dysfunction, cerebral oedema, and functional deficits has been described in stroke [34-36, 38].

Having established the presence of neurogenic inflammation and the role of SP in brain injury following trauma, subsequent experimental studies have examined the efficacy of blocking the effect of SP. An NK1 tachykinin receptor antagonist administered at 30mins following trauma conferred protection from injury-induced BBB permeability alterations, cerebral oedema (Figure 2) and functional deficits [12] in rodent models. Moreover, the therapeutic window was shown to be at least 12h following trauma with improvements in neurological

outcome and a reduction in neuronal injury still observed with such delayed treatment [32]. Studies using capsaicin pre-treatment to deplete the neuropeptides before injury have produced comparable improvements in BBB status, cerebral oedema and neurological outcome [33]. Taken together, such studies illustrate the involvement of neuropeptides in the genesis of cerebral oedema following acute injury to the brain [33] and demonstrate that the neuropeptide SP is primarily responsible for the development of neurogenic inflammation and subsequent alterations in BBB permeability and cerebral oedema which are observed in the setting of experimental acute brain injury [12, 32].

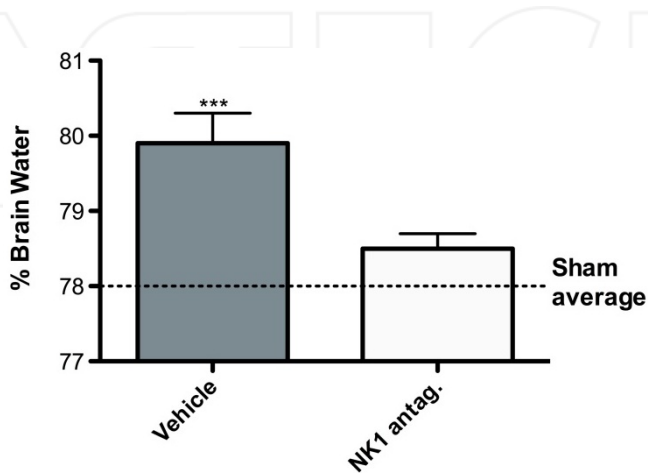


Figure 2. Cerebral oedema, as measured by wet weight dry weight, at 5h following diffuse traumatic brain injury in rats. Treatment with an NK1 antagonist significantly reduced cerebral oedema following trauma.

The efficacy of NK1 tachykinin receptor antagonists in treating BBB dysfunction and cerebral oedema in rodent TBI models is encouraging. However, given the disappointing lack of clinical translation of treatments shown to be neuroprotective in rodent models, it is becoming increasingly important to validate agents of promise in large animal models before any progression to clinical studies. Furthermore, we have recently reported that rodent TBI models do not produce consistent elevations in ICP in the absence of mass lesions, making them inappropriate for studying the evolution of increased ICP [48]. Accordingly, we have recently evaluated the efficacy of NK1 tachykinin receptor antagonists in an ovine model of TBI. This animal model incorporates a large gyrencephalic brain with large white matter domains and a significant tentorium cerebelli, features that are comparable to the human brain and essential in order to effectively study cerebral oedema and ICP dynamics. Administration of an NK1 tachykinin receptor antagonist at 30 mins following TBI produced a profound reduction in ICP by 4 h after injury (Figure 3) as compared to vehicle treated controls [6].

Blocking the action of SP with an NK1 antagonist significantly reduce ICP following trauma.

The NK1 tachykinin receptor antagonists have now been shown to be efficacious in reducing the BBB permeability, cerebral oedema, rises in ICP and functional deficits associated with TBI

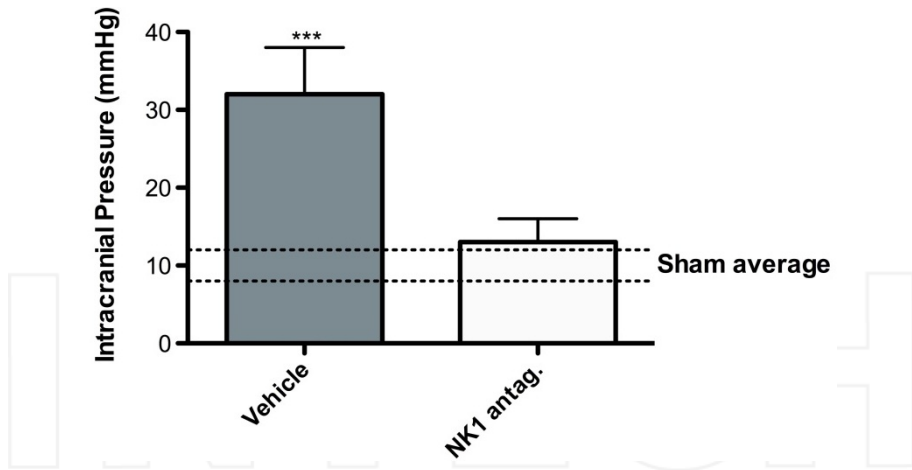


Figure 3. Intracranial pressure as measured at 4h following ovine traumatic brain injury.

in experimental models. Such studies have validated the use of NK1 tachykinin receptor antagonists in multiple models of trauma and in multiple species, including large animal models with a gyrencephalic brain. These studies in rodent and ovine models of TBI consistently demonstrate that SP release is a ubiquitous feature of acute injury to the brain. In addition, by using inactive enantiomers of the active ligands as well as a number of different structural antagonists, they emphasise that the efficacy of NK1 tachykinin receptor antagonists is a class effect rather than simple drug-specific effect. One can only conclude that, at least in these animal studies, the improvements observed were dependent upon inactivation of SP and its NK1 receptor.

A limited number of studies have also investigated the presence of neurogenic inflammation in human patients with TBI. In a cohort of patients who had sustained a TBI and subsequently died and undergone post-mortem and detailed neuropathological examination, SP immunoreactivity was increased compared to control cases [49]. Specifically, increased SP immunoreactivity was observed in the perivascular tissue surrounding the microvessels, and in particular around the post-capillary venules. Increases in SP were also observed in the perivascular axons, cortical neurons and astrocytes. The authors concluded that mechanical activation of the perivascular neurons initiated SP release and that SP played a significant role in initiating neurogenic inflammation following human TBI.

7. Conclusions

SP, through the process of neurogenic inflammation, has long been known to cause plasma extravasation and swelling in peripheral tissues. However, it has only been in recent years that the concept of neurogenic inflammation has been extended to the CNS and its role in BBB dysfunction and cerebral oedema appreciated. Furthermore, therapeutic intervention studies

that have blocked the action of SP have demonstrated profound reductions in BBB permeability, cerebral oedema, ICP and functional deficits in multiple species and models of TBI. Clearly, modulation of neurogenic inflammation using tachykinin NK1 receptor antagonists provides a novel therapeutic target for the treatment of cerebral oedema and elevated ICP in the setting of TBI, and other acute injuries to the brain.

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