

Review

The Role of Substance P and NK1 Receptors in Mild to Severe Traumatic Brain Injury: From CTE to ICP

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Abstract: Binding of substance P to the tachykinin NK1 receptor is involved in numerous physiological and pathophysiological processes ranging from modulation of sensory and motor function to inflammation, cancer, and brain injury, amongst others. NK1 antagonists therefore have enormous potential as a therapeutic intervention in a wide variety of human disease states, albeit that the clinical potential is yet to be fully realised. In the current review, the role of substance P in the pathophysiology of traumatic brain injury (TBI) will be discussed, summarising both experimental and clinical observations in mild, moderate, and severe TBI. In addition, the potential for NK1 antagonists to be a valuable therapeutic intervention against chronic traumatic encephalopathy (CTE) after repeated concussive brain injury as well as raised intracranial pressure (ICP) following severe TBI will be addressed, highlighting the various pathophysiological processes that are attenuated by the intervention.

Keywords: NK1 receptor; substance P; neurotrauma; oedema; intracranial pressure; chronic traumatic encephalopathy



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1. Introduction

Traumatic brain injury (TBI) is an acquired insult to the brain caused by external mechanical impact and/or acceleration forces that result in transient or permanent neurological dysfunction. It is the leading cause of death between the ages of 10 and 45 [1] and has for many years been termed the silent epidemic [2], a term which has become even more relevant today given the recently accepted association between repeated mild TBI (i.e., concussion) and delayed neurodegeneration [3].

Injury to the brain with subsequent neuronal cell dysfunction or cell death occurs through two major mechanisms after TBI, known, respectively, as primary injury and secondary injury [4]. Primary injury encompasses the mechanical events that occur at the time of the traumatic event and includes such things as tissue tearing, stretching, skull fracture, and haemorrhage. The only options available to attenuate such primary injuries are preventative in nature, and examples include the wearing of seat belts, helmets, and the use of air bags in motor vehicle design. In contrast, secondary injury is made up of biochemical and physiological events that occur in the minutes, hours, and days after the injury and result in delayed damage to neurones with time. Given that secondary injury develops over time, there is therefore a time window in which to attenuate or even prevent secondary injury and potentially improve the outcome. What is critical is identifying the relevant secondary-injury factors that cause irreversible tissue damage and developing appropriate anti-factors to attenuate the resultant brain damage.

While numerous secondary-injury factors have been identified, including excitotoxicity, reactive oxygen species, calcium accumulation, and mitochondrial dysfunction, amongst others [4], one secondary-injury factor has recently been shown to play a role at all

injury levels, including repeated mild TBI with delayed neurodegeneration and in severe TBI and its effects on intracranial pressure (ICP). That injury factor is the neuropeptide substance P.

Substance P is a member of the tachykinin protein family that also includes neurokinin A and neurokinin B [5]. Like neurokinin A, substance P is derived from the pre-protachykinin A gene by alternative splicing. While widely distributed throughout the central and peripheral nervous systems, in the brain it is more abundant in the grey matter than in the white matter and can be found in the cortex, hippocampus, hypothalamus, amygdala, basal ganglia, and caudate nucleus. Its effects are mediated by the tachykinin NK receptors, and while substance P has some affinity for the NK2 and NK3 receptors, it preferentially binds to the NK1 receptor [5]. The binding affinity of substance P for the NK1 receptor is so much greater than for other tachykinins that the receptor is also known as the substance P receptor [6]. The general structure, function, and actions of the NK1 receptor have been previously described in detail elsewhere and will not be repeated herein (see [6–8] for excellent reviews). However, briefly for the purposes of this review, there is both a full-length isoform of the NK1 receptor and a truncated version. The full-length isoform is expressed at much higher concentration in the brain [9] and therefore is the most critical from the standpoint of brain function. In addition to autoreceptors on neurones, these receptors are expressed on astrocytes, microglia, and endothelial cells as well as various types of inflammatory immune cells. Transduction of substance P/NK1 signalling occurs via G proteins and leads to the regulation of various ion channels, enzyme activities and alterations in gene expression [5,6]. With the NK1 receptor having different active conformations, each having a different affinity for particular agonists, the receptor conformation and the type of ligand determine the specific G protein being regulated [10]. Binding of substance P to brain NK1 receptors after TBI has been shown to be integral to a variety of pathophysiological processes and will be discussed according to injury severity.

2. Mild TBI

Mild TBI, encompassing concussion, is any traumatic injury to the brain that results in immediate and transient impairment of brain function, including disturbances of vision, hearing, and/or equilibrium and potentially alterations of consciousness, amongst others. While the physical symptoms such as blurred vision, dizziness, and nausea, as well as any cognitive deficits and behavioural changes, usually resolve in a relatively short time frame, these latter symptoms may nonetheless persist in some individuals [11]. However, because few symptoms are visible to the casual observer in the immediate timeframe after impact, concussion was historically considered as somewhat of an innocuous event. Recent evidence, however, has shown that its occurrence can produce persistent functional disability in some individuals [11], and even later neurodegeneration [12]. Particular attention has been directed to a specific form of neurodegeneration known as chronic traumatic encephalopathy (CTE), which has been widely reported in professional athletes and military personnel who have been exposed to repeated head impacts [12].

The first report of substance P in concussion [13] simply demonstrated that the neuropeptide was released after a concussive impact and could be observed by immunohistochemistry in brain perivascular neurones and in astrocytes. Given the known role for substance P in oedema formation [14], the authors proposed that release of the neuropeptide from perivascular neurones sensitises cerebral blood vessels for increased permeability in the event of a second concussive impact, thus facilitating potentially profound oedema formation (second impact syndrome).

Subsequent studies in concussion have focussed on the potential role of substance P in repeated impacts and the development of CTE. CTE is characterised by the accumulation of phosphorylated tau protein tangles, initially appearing in perivascular neurones in areas of the brain which are subject to high mechanical stress with head impact (such as the depths of the sulci) and then spreading to other regions of the brain with time [15]. The severity of this tau pathology correlates with cognitive impairments that are observed as

the disease progresses [16]. Notably, increased vascular permeability has been reported after exposure to repeated head impacts [17], implying a role for neuroinflammation in the pathophysiology.

In a comprehensive study using a variety of experimental TBI models, Corrigan and colleagues [18] demonstrated that brain substance P expression was increased following a single concussive injury but did not result in tau hyperphosphorylation. However, following three concussive injuries inflicted within a 10-day period, brain substance P expression was markedly increased and was associated with profound perivascular tau hyperphosphorylation, the hallmark of CTE. Indeed, the level of tau hyperphosphorylation after three closely timed concussive events was equivalent to that observed following a moderate TBI. Administration of a TRPV1 receptor (mechanoreceptor) antagonist prior to the induction of head injury prevented tau phosphorylation, presumably by inhibiting the release of substance P. However, when the TRPV1 antagonist was administered after the head injury, there was no such inhibition, suggesting that substance P release had already been initiated by the mechanical insult. In contrast, administration of the substance P NK1 receptor antagonist, EUC001 [19], after the brain injury attenuated tau hyperphosphorylation by moderating the activity of several key kinases associated with tau phosphorylation, including Akt, ERK1/2, and JNK [20–22]. Notably, confocal microscopy images of the cortical neurones demonstrated co-localisation of the neuronal phosphorylated tau and NK1 receptors (Figure 1), supporting the pharmacologic data demonstrating a link between NK1 receptors and tau hyperphosphorylation. Notably, administration of the NK1 antagonist at 30 min after mild, blast-induced injury in mice (a known cause of CTE) attenuated the post-traumatic tau phosphorylation for up to 28 days after the injury [18]. To the best of our knowledge, human studies of post mortem CTE are yet to examine the relationship between substance P, NK1 receptors, and accumulation of phosphorylated tau.

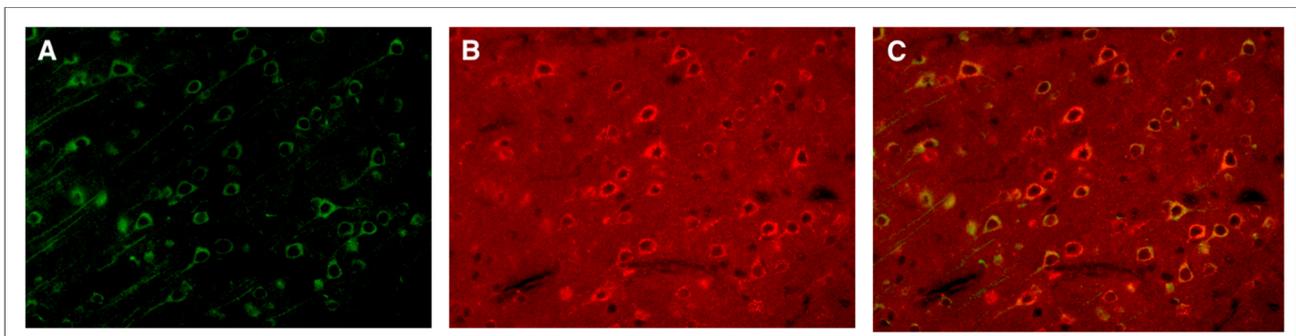


Figure 1. Confocal microscopy images of rat cortical neurones 24 h after TBI showing (A) AT180 phosphorylated tau, (B) NK1 receptors, and (C) the co-localisation of the two in the merged image. Adapted from [18] under Creative Commons licence.

Neuronal NK1 receptors therefore contribute to two critical events after repeated concussive injury. The first is that with subsequent concussive injuries, NK1 autoreceptor activation further amplifies the release of substance P with each injury, thus allowing the neuropeptide to radiate away from the vasculature, potentially activating up to five times more neurones expressing NK1 receptors [23]. Secondly, more intense or repeated activation of the neuronal NK1 receptor also results in increased kinase activity, including those kinases that have been linked to increased phosphorylation of tau protein [24]. Protein phosphatases normally dephosphorylate tau to prevent tau protein aggregation. However, substance P induces membrane translocation of protein phosphatase PPA2 [25] such that reduced cytosolic phosphatase activity may be exceeded by the increased kinase activity resulting in the accumulation of tau protein aggregates. Both these events can be prevented with the administration of a cell-permeable (to cross the blood–brain barrier) NK1 antagonist.

3. Moderate TBI

Moderate TBI was where a role for neurogenic inflammation was first identified [26,27]. In these studies, transient depletion of neuropeptides from neuronal C fibres using capsaicin pre-treatment led to reduced BBB permeability, reduced oedema formation, and improved functional outcome after TBI compared to untreated controls. While substance P was strongly implicated in these events, a series of subsequent studies characterised the precise role of substance P and NK1 receptors both in experimental models of TBI and in clinical TBI [28–31]. These studies demonstrated that substance P is released by perivascular neurones, particularly those that have been stressed by the mechanical events associated with TBI [31]. Substance P preferentially binds to NK1 receptors in the vicinity, including those located on the vascular endothelium, leading to a localised increase in BBB permeability and an associated movement of blood proteins such as albumin from the vasculature into the brain parenchyma. This creates an osmotic gradient which drives movement of water from the vasculature into the brain tissue causing vasogenic oedema [32]. Not only does albumin translocation across the barrier create an osmotic gradient, translocation of albumin into the brain is also known to activate a tissue inflammatory response [33], which further exacerbates the BBB permeability, enhances recruitment of inflammatory cells, and further increases oedema formation [34]. Together with the primary mechanical insult, this neuroinflammatory response ultimately leads to neuronal cell damage and functional deficits, both motor and cognitive. There is considerable evidence suggesting that chronic neuroinflammation involving a variety of glial cells may also lead to later neurodegeneration, including the tau phosphorylation typically observed in CTE [18,34].

With clear evidence that substance P is increased after moderate TBI and binds to NK1 receptors to mediate some of its effects, several experimental studies have characterised the potential role of NK1 antagonists as neuroprotective agents [35]. A variety of substance P NK1 receptor antagonists have been used in these studies to demonstrate the central role of the NK1 receptor in TBI and its efficacy as a therapeutic intervention. Initial studies focussed on the highly selective NK1 receptor antagonist N-acetyl L-tryptophan 3,5-bis (trifluoromethyl) benzyl ester (L-732,138) and its non-permeable form, N-acetyl L-tryptophan (NAT). Both were shown to inhibit BBB permeability after TBI in an identical dose-dependent manner and were equally effective at improving post-traumatic oedema and post-traumatic functional outcomes when administered after trauma. Notably, the D isomer of NAT was an ineffective relative to the L isomer, suggesting that the neuroprotective effects were receptor mediated [29]. However, the effectiveness of the non-permeable NAT was limited to the period immediately after TBI when the BBB was transiently open. Later experimental TBI studies have adopted other, more cell-permeable NK1 antagonists including the Merck compound L-733,060 [36] and the Roche compound EUC-001 [19]. The move away from NAT in experimental studies was useful not only to address its inability to cross the intact BBB but also because of controversies surrounding its classification as an NK1 antagonist. While some studies have definitively shown that NAT binds to and inhibits the NK1 receptor as well as presynaptic substance P release [37], others have been unable to confirm NK1 receptor binding [38]. In circumventing these issues, studies using alternative BBB permeable NK1 antagonists may better facilitate clinical translation, particularly EUC-001, which is a highly selective antagonist of the human NK1 receptor, is a water-soluble yet membrane-permeable compound, and has few potential drug–drug interactions [19].

Irrespective of the NK1 antagonist that has been utilised in the experimental studies, these antagonists have universally shown profound neuroprotective effects when administered following moderate TBI (see [39] for review). Moreover, these neuroprotective effects were apparent irrespective of the animal species used or the model of injury (focal versus diffuse) that was employed. When administered as a parenteral bolus (either IV or IP) at 30 min after injury, NK1 antagonists significantly improved both motor and cognitive deficits over the first 2 weeks after trauma [30,40]. This neuroprotection was independent of sex, with females also responding positively to the NK1 antagonist [28]. In mice, knockout

of SP synthesis was equivalent to administering an NK1 antagonist in terms of neuroprotective efficacy [40], supporting previous studies showing that preinjury SP depletion with capsaicin was profoundly neuroprotective [26]. NK1 antagonists reduced cell death in both the hippocampus and in the cortex, as well as axonal injury in the corpus collosum [28,29], and were shown to reduce lesion volumes in focal models of injury [40].

While initial studies all administered a bolus of NK1 antagonist in the first hour after injury, it has been shown that cell-permeable forms of the NK1 antagonist are efficacious even when administered as late as 12 h after injury [29]. Notably, efficacy with a non-membrane-permeable antagonist was limited to the first 5 h, corresponding to when the BBB after TBI is known to be open to large protein molecules [41]. Thereafter, the BBB gradually closes to large protein molecules, thus necessitating the use of membrane-permeable versions of the antagonist.

Various mechanisms have been identified by which NK1 antagonists might improve cell survival after TBI and improve functional outcomes [40]. In addition to reducing aspects of neurogenic inflammation (such as increased BBB permeability and vasogenic oedema), NK1 antagonists have been shown to reduce oxidative stress, preserve mitochondrial membrane potential, inhibit mitochondrial cytochrome c release, inhibit apoptosis, inhibit classical neuroinflammation, preserve ATP levels, inhibit non-apoptotic programmed cell death [42], and increase intracellular free magnesium concentration [43]. Thus, NK1 antagonists act on multiple known secondary-injury pathways to confer neuroprotective effects after moderate TBI (Figure 2).

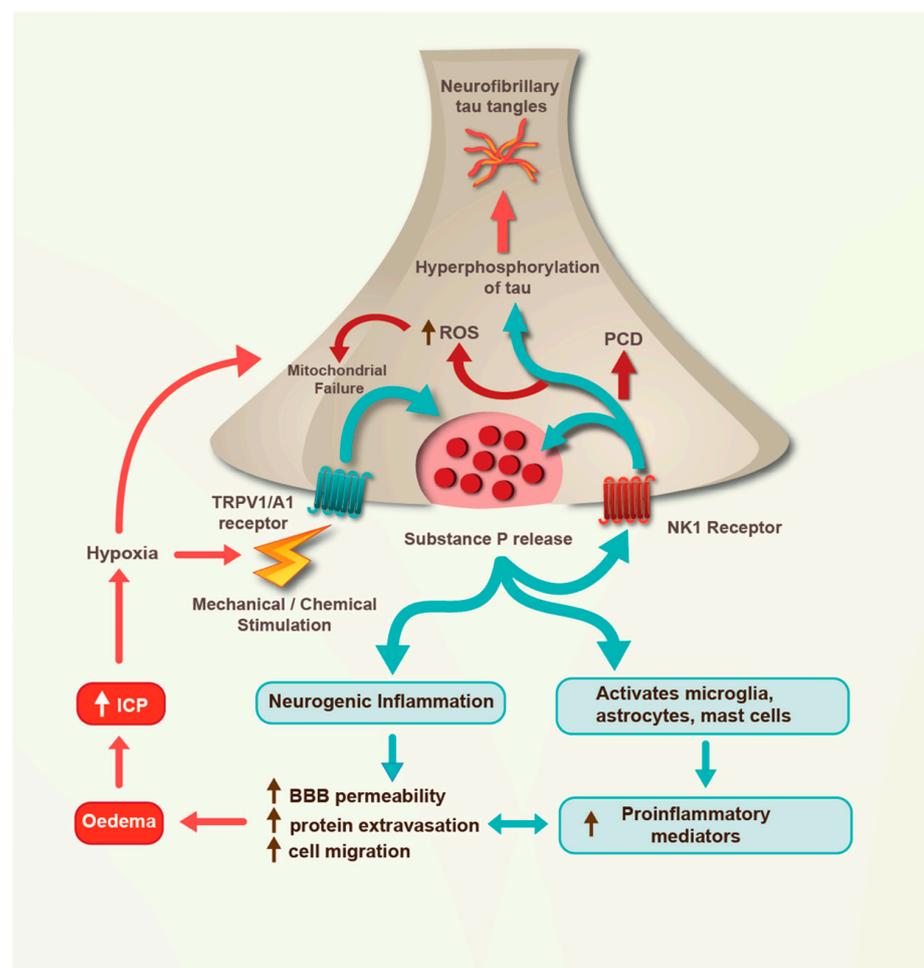


Figure 2. Schematic demonstrating release of substance P and the post-traumatic pathophysiological events activated from binding with the NK1 receptor. With activation of the mechanosensitive TRP receptors, substance P is released. Binding of substance P to the neuronal NK1 autoreceptor not only

upregulates further substance P release but also activates kinases that phosphorylate tau. With repeated TRP stimulation, the rate of tau phosphorylation exceeds the ability of phosphatases to dephosphorylate tau, resulting in the formation of neurofibrillary tau tangles. Released substance P also binds to NK1 receptors on astrocytes, microglia, and vascular endothelial cells, resulting in inflammation (blue arrows). At more severe levels of TBI, additional secondary-injury pathways are activated (red arrows), leading to oedema and increased ICP, as well as increased neuronal reactive oxygen species (ROS), mitochondrial failure, and programmed cell death (PCD).

4. Severe TBI

Severe TBI typically results in profound neurological deficits in survivors because of extensive tissue damage caused by both primary and secondary injury mechanisms. Both clinical studies of blood substance P and experimental TBI studies have implicated substance P in the secondary injury process following severe injury. Indeed, serum levels of substance P have been recently shown to be a predictor of outcome following severe TBI [44–46]. Higher levels of serum substance P were reported on day 1 in non-surviving patients compared to survivors, with an ability to predict 30-day mortality reported [44]. No differences were observed between male and female patients, and a negative correlation between day 1 serum substance P levels and neurological outcome in survivors was noted. A subsequent study by the same group showed that elevated levels of serum substance P persisted over the entire first week after severe injury, and the highest levels again predicted mortality [45]. Studies in children have reported similar increases in serum substance P after injury, with high levels of the neuropeptide being associated with increased mortality [46]. Indeed, serum substance P concentration had the same power to predict risk of death in children as did the Sequential Organ Failure Assessment scores and the Paediatric Clinical Illness Score. The negative correlation between serum substance P and neurological outcome was again confirmed, although in children, it extended across mild to severe TBI [46]. Such increases in serum substance P after TBI were accompanied by serum hypomagnesemia and occurred irrespective of the presence of intracranial lesions [47].

In terms of brain pathophysiology, one secondary-injury factor that is associated with more death and disability following severe TBI than any other is increased intracranial pressure (ICP). Increased ICP is the result of increased fluid volume in the enclosed skull, and while increased fluid volume can be caused by mass haemorrhage or by vasodilation, it is the movement of water from the vasculature to the brain parenchyma (vasogenic oedema) that is the major driver of increased ICP. As the tissue pressure inside the skull increases, blood vessels become compressed, thus limiting the supply of oxygen to the tissues (hypoxia) and in some cases preventing adequate tissue perfusion (ischemia). Extensive brain tissue damage results. Death can result when the critical centres for control of respiration and cardiac function in the brainstem are compressed.

The role of the substance P/NK1 axis in oedema formation has been well characterised in moderate TBI [32], and while studies in rodent models of TBI attempted to ascertain their role in development of increased ICP, limitations in studying ICP with the rodent models proved problematic [48]. An existing sheep model of TBI has been shown to reproduce many of the characteristics of clinical TBI, particularly the changes in ICP and brain tissue oxygenation that follows injury [49], and thus facilitated studies of NK1 antagonists. In a series of studies examining moderate to severe TBI, the increased ICP that is typically produced after TBI was rapidly reduced by NK1 antagonists administered IV at 30 min after injury [50]. Indeed, ICP was reduced to normal levels within hours of administration. Similar changes were observed in brain tissue oxygenation, which had been previously shown to be clearly related to ICP levels [49]. Administration of an NK1 antagonist at 30 min after trauma resulted in a return of brain tissue oxygenation levels back to near normal within hours of administration, slightly after and seemingly in response to the changes in ICP [51]. The effects of the NK1 antagonist on ICP were shown to be superior to mannitol, which is used clinically to reduce ICP. Mannitol is an osmotic agent that draws water out of the tissue by increasing vascular

osmotic pressure. However, in the presence of an open BBB, mannitol has been known to enter the brain parenchyma and cause a rebound increase in ICP. The mechanism of NK1 antagonists is to reduce BBB permeability and inhibit vasogenic oedema, thereby eliminating the possibility of any rebound increases in ICP.

In the rodent models of TBI used for the NK1 studies, oedema development was rapid and achieved maximal levels within the first 24 h [52]. Similarly, in the sheep model of TBI, ICP increased rapidly after trauma and achieved maximal levels within the first 24 h [49]. Since repeated dosing with an NK1 antagonist in moderate rodent TBI did not prove advantageous in further reducing oedema or improving functional outcome (Vink, unpublished results), repeated dosing with an NK1 antagonist in the sheep model of TBI was therefore considered unnecessary. However, not all acute brain injury models have maximal ICP in the first 24 h. Using a permanent middle cerebral artery occlusion stroke model in sheep, Sorby-Adams [53] demonstrated delayed and persistent increases in ICP could be attenuated with administration of the NK1 antagonist, EUC-001. When administered as a single bolus at 4 h after induction of stroke, the NK1 antagonist did prevent an increase in ICP; however, the effects were transient and in keeping with the half-life of the drug. When administered a second and third dose at 5 h intervals after the first, ICP was better controlled and remained in the normal range for the duration of the experiment. Notably, repeated administration of the NK1 antagonist was as effective at reducing ICP as was surgical decompressive craniotomy. Repeated administration of the NK1 antagonist had additional benefits compared to decompressive craniotomy, with greater reductions in oedema, as well as albumin extravasation and perivascular NK1 receptor and caveolin-1 immunoreactivity [53], a protein marker for caveolae [54]. Thus, for efficacy in controlling persistently elevated ICP that occurs in some forms of acute brain injury, including severe clinical TBI, repeated administration of an NK1 antagonist may be required.

Although the mechanisms by which NK1 antagonists attenuate protein translocation after TBI are unknown, caveolae have been implicated [34,53]. Caveolae are membrane invaginations that have a key role in transcytosis of proteins, including albumin, across the BBB [55]. Indeed, it has been previously shown that caveolin-1 knockout mice are unable to transcytose albumin [56]. Moreover, caveolin-mediated transcytosis depends on neither the physical breakdown of the barrier nor of the endothelial tight junctions. Thus, an increased BBB permeability as reflected by increased albumin translocation may be observed in the absence of endothelial tight junction failure. Previous reports have confirmed that endothelial tight junctions are intact in the hours following TBI, despite the concurrent increase in BBB permeability and in protein translocation [54,57] and the associated development of vasogenic oedema [58]. Notably, increased caveolin-1 expression occurs at this time [54], with ultrastructural studies confirming increased endothelial caveolae in vascular segments showing loss of BBB integrity, as well as increased vesicular formation after TBI [59]. NK1 receptors are located in caveolae [60,61], and stimulation of these NK1 receptors is known to cause protein kinase C to relocate to caveolae [62] and facilitate their internalisation [63], the first step in protein transcytosis. It is therefore reasonable to suggest that caveolae-located NK1 receptor activation may be the mechanism responsible for the increase in BBB permeability and protein translocation that occurs in the immediate hours after TBI. Inhibition of transcytosis by NK1 antagonists would therefore prevent translocation of proteins, prevent further vasogenic oedema formation, and accordingly any associated increases in ICP.

5. Conclusions and Future Directions

Evidence to date shows that binding of substance P to the NK1 receptor plays a central role in pathophysiological events following traumatic brain injury. This has now been confirmed by multiple laboratories in various small and large animal experimental models of TBI including focal, diffuse, and blast injury models (Table 1), in clinical TBI, as well as in other forms of acute brain injury such as stroke. Since substance P release is initiated by mechanical stimulation of perivascular neurones, NK1 receptor activation represents one of the earliest events initiated by the traumatic insult, subsequently facilitating multiple

secondary injury cascades. What is unique about the release of substance P after TBI is that its release is modulated by neuronal NK1 autoreceptors such that the frequency and intensity of mechanical stimulation determines the degree and anatomical distribution of NK1 receptor activation [23]. Hence, the response to substance P release varies with differing injury severity and frequency.

The next phase in the development of NK1 antagonists in TBI is the clinical trial phase, although phase I trials have been successfully completed with phase II trials pending [64]. The general difficulties associated with pursuing clinical trials in TBI have been critically examined elsewhere [65] and need not be reiterated here. However, there are specific issues related to clinical trials of NK1 antagonists that are highly relevant to any attempt at translation. Most significantly, dose seems to require careful calibration such that the success of pre-clinical studies can be translated to the clinical context. For example, clinical trials of emesis have demonstrated that a dose of 125 mg of aprepitant is sufficient to observe therapeutic effects [66]. However, studies examining the efficacy of aprepitant as an antidepressant showed a beneficial action at 300 mg/day but not at 160 mg/day [67,68]. The lower dose has been shown to achieve a central NK1 receptor occupancy greater than 90% [69], which while sufficient as an antiemetic, was insufficient for antidepressant effects. Antidepressant activity is thought to require a central NK1 receptor occupancy approaching 100% [68], which, given the excellent safety profile of this class of compounds in clinical trials to date, would not be expected to result in any further significant side effects. Thus, different levels of central NK1 receptor occupancy are required for efficacy in different pathological conditions, and this needs to be carefully established and controlled for in clinical trials. In the absence of PET studies of receptor occupancy, the plasma concentration of the drug can be used as a guide to central receptor occupancy [70].

A variety of factors can impact on plasma concentration of the NK1 antagonist. Being lipophilic, the drug has a propensity to accumulate in high-lipid-content tissues, which is clearly essential for central penetration. However, adipose tissue is also high in lipid content, and when BMI is high, it becomes a “sink” for the compound, reducing plasma concentration to potentially below the therapeutic threshold. Scaling dose for weight is generally adopted as a means to address this concern, but pharmacokinetic studies are essential to ensure effective plasma concentration of the drug is both achieved and maintained. Notably, experimental animal studies have all adopted bolus IV injection as the route of administration as opposed to slow infusion, primarily to rapidly achieve therapeutic plasma levels. Repeated administration according to the drug half-life then maintains the plasma levels above the therapeutic threshold. Clinical trials will require pharmacokinetic studies to ensure that plasma levels in individuals of varying weights do achieve plasma therapeutic concentrations. A fixed dose in a 90 kg individual will be just 50% of the same fixed dose in a 45 kg individual, enough to result in suboptimal levels and guarantee no beneficial effect.

In choosing an appropriate NK1 antagonist for use in TBI trials, the agent will need to be highly selective for the full-length isoform of the human NK1 receptor, be BBB permeable, preferably be water-soluble to simplify administration, and have minimal side effects, particularly on the cytochrome P450 family of liver enzymes. Many drugs used in the management of severe TBI, including midazolam and corticosteroids, are metabolised by the cytochrome P450 enzymes. This interaction needs to be avoided so as not to interfere with routine TBI management. While aprepitant and its cell-permeable form fos-aprepitant have been widely used in clinical trials of NK1 antagonists in other conditions [71], they would be largely unsuitable for use in TBI because they induce/inhibit the cytochrome P450 enzyme family. Fortunately, other suitable NK1 antagonists without this limitation have been developed [19]. There is a great sense of optimism that carefully chosen NK1 antagonists [19] in carefully designed trials of severe TBI with clear, unambiguous endpoints will prove successful. Trials in mild TBI, or concussion, are more challenging in that currently CTE can only be diagnosed post mortem. However, the development of suitable endpoints in the form of surrogate markers, including plasma biomarkers, will greatly facilitate progress in this area.

Table 1. Summary of major findings demonstrating a role for substance P and NK1 antagonists in TBI. SP = substance P; TBI = traumatic brain injury; BBB = blood–brain barrier; ICP = intracranial pressure.

Condition	Species	Model	Notable Observations	Citation
Mild TBI	Rat	Single weight drop	Increased perivascular and astrocytic SP immunoreactivity	Donkin et al., 2004 [13]
	Rat	Repeated weight drop	Neuronal tau phosphorylation after injury is inhibited by NK1 antagonist	Corrigan et al., 2021 [18]
	Mouse	Blast	NK1 antagonist reduced tau phosphorylation at 28 days after injury and improved functional outcome	Corrigan et al., 2021 [18]
Moderate TBI	Rat	Weight drop	Capsaicin pre-treatment reduces brain oedema and functional deficits	Vink et al., 2003 [27]; Nimmo et al., 2004 [26]
	Rat	Weight drop	NK1 antagonist increases brain free magnesium after TBI	Vink et al., 2004 [43]
	Rat	Weight drop	Increased brain SP immunoreactivity and serum SP after injury; NK1 antagonist reduces post-traumatic BBB permeability and oedema, and improves functional outcome	Donkin et al., 2009 [30]
	Rat	Weight drop	NK1 antagonist reduces axonal injury and improves functional outcome even when administered up to 12 h post-trauma	Donkin et al., 2011 [29]
	Rat	Weight drop	NK1 antagonist reduces axonal injury and improve functional outcome in female animals	Corrigan et al., 2012 [28]
	Rat	Weight drop	NK1 antagonists inhibit microglial proliferation	Carthew et al., 2012 [72]
	Mouse	Cortical impact	NK1 antagonist and SP deletion inhibits post-traumatic oxidative stress, apoptosis, neuroinflammation, and cell death; improves functional outcome	Li et al., 2019 [40]
Severe TBI	Human	Clinical	Perivascular SP immunoreactivity is increased after trauma and may be released in response to neuronal stress	Zacest et al., 2010 [31]
	Sheep	Captive bolt	NK1 antagonist reduces post-traumatic elevated ICP	Gabrielian et al., 2013 [50]
	Sheep	Captive bolt	NK1 antagonist reduces post-traumatic elevated ICP and improves brain oxygen	Gabrielian et al., 2017 [51]
	Human	Clinical	Elevated serum SP associated with injury severity and mortality in adults	Lorente et al., 2015 [44]; 2017 [45]
	Human	Clinical	Elevated post-traumatic serum SP in children	Zhou et al., 2021 [46]
	Human	Clinical	Elevated serum SP part of a multi-staged neuropeptide response after TBI	Alves et al., 2022 [47]

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