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Chronic traumatic encephalopathy: genes load the gun and repeated concussion pulls the trigger

Robert Vink*, Frances Corrigan

The association between traumatic brain injury (TBI) and an increased risk of neurodegeneration has been recognized for some decades now (Faden and Loane, 2015), with recent evidence suggesting that a history of TBI, either as repeated concussive/mild TBI insults typically experienced by some athletes or less commonly as a single moderate/severe injury, may be linked with an increased risk of developing a specific form of neurodegeneration known as chronic traumatic encephalopathy (CTE) (McKee et al., 2016). The pathognomonic lesions of CTE are hyperphosphorylated tau aggregates, initially in neurons and astrocytes close to blood vessels at the base of the sulci, but later spreading throughout the brain (McKee et al., 2016). Recent work has focused on developing diagnostic criteria for traumatic encephalopathy syndrome, the clinical disorder associated with CTE, which is thought to encompass cognitive impairment and/or neurobehavioral impairment characterized by explosiveness, impulsivity and emotional lability (Katz et al., 2021). However, this work has yet to be validated with CTE currently only being definitively diagnosed post-mortem using well defined pathological criteria (McKee et al., 2016).

The mechanistic link between TBI and the development of CTE has proven elusive, although it is widely believed that the mechanical events of TBI, that are known to be amplified at the base of the sulci, are the likely trigger that initiates its development. We have recently confirmed this association by showing that repetitive mild TBI stimulates brain mechanoreceptors that initiate release of the neuropeptide substance P (SP), which activates a number of kinases and results in hyperphosphorylation of tau protein (Corrigan et al., 2021). Cerebral blood vessels are richly innervated with SP containing neuronal C fibers, and their repeated stimulation triggers perivascular release of the neuropeptide which initiates a positive feedback loop that not only potentiates SP release, but also markedly extends the distance that SP is able to diffuse away from the point of release at the blood vessels (Corrigan et al., 2016). Notably, inhibition of SP release by blocking the transient receptor potential vanilloid 1 mechanoreceptor at the time of injury, or inhibition of SP binding to its NK1 receptor after injury, inhibits phosphorylation of tau protein and improves neurological outcomes (Corrigan et al., 2021).

Aside from activating kinases known to be associated with tau phosphorylation, SP is a well-known potent mediator of inflammation (Corrigan et al., 2016). It directly activates microglia, astrocytes, mast cells and leukocytes resulting in the production of various inflammatory mediators including cytokines (interleukin 1, interleukin 6, CCL2), prostaglandins, thromboxane derivatives, kinins, histamine, and nitric oxide (Corrigan et al., 2016). The neuropeptide is also known to increase permeability of the blood brain barrier by upregulating extravasation of vascular proteins, including albumin, which in itself can initiate an inflammatory response. Inflammation has been shown to be a key factor in the development of dementia (Ransohoff, 2016), including CTE. Specifically, cytokines such as CCL2 have been shown to be associated with recruitment of microglia and macrophages and in the development of phosphorylated tau pathology after repeated mild TBI (Cherry et al., 2020), while increased blood-brain barrier permeability has been widely reported following repeated mild TBI and is thought to potentiate ongoing neuroinflammation. Reactive astrogliosis post-TBI is associated with the loss of aquaporin channels, impairing protein clearance via the glymphatic system further contributing to the accumulation of neurotoxic tau species (Graham and Sharp, 2019). Thus, SP release not only leads to perivascular tau hyperphosphorylation, but also initiates and potentiates neuroinflammation (**Figure 1**).

While SP release is clearly initiated by concussive events, not everyone who has been subject to repetitive mild TBI will show signs of neurodegeneration in their lifetime. This is despite the fact that repeated mild TBI would trigger the onset of the neuroinflammatory and tau related events that are associated with the development of CTE (Corrigan et al., 2021). Notably, we do not have an epidemic of CTE associated with the increased participation in contact sports, with the incidence of the disease in the general community having been reported to be extremely low (Postupna et al., 2021). What then accounts for the susceptibility of some individuals to CTE? There is evidence from a number of studies that suggest genetic factors may play an important role in neurodegeneration. Previous studies in Alzheimer's disease have shown that multiple genetic factors may influence disease onset, with the presence of the apolipoprotein E ε4 allele being singled out as one genetic factor that induces a proinflammatory state and promotes tau pathology (Friedberg et al., 2020). We posit that a similar influence of genetic factors will determine ones' susceptibility to CTE, but not in a binary (yes or no) manner but rather by influencing age of clinical symptom expression. Indeed, one genetic risk factor has already been identified in studies of CTE. A variation in the transmembrane protein 106B gene was shown to predict increased CTE pathology and neuroinflammation amongst athletes with CTE, and the associated presence of dementia, but notably the presence of the gene variation was no different between athletes with CTE compared to those without (Cherry et al., 2018).

From adulthood, the brain is essentially degenerating and all individuals would be expected to express clinical signs of neurodegeneration at some point in their lifetime if indeed they lived long enough. The reality is that most people will die from other causes before any neurodegeneration expresses itself in clinical form. However, while some individuals may live to 100 and not show any clinical signs of neurodegeneration, others will show clinical signs of neurodegeneration as early as 65. It is reasonable to assume that genetic and environmental factors influence age of clinical onset. Consider that exposure to repetitive mild TBI is an environmental factor that accelerates neurodegeneration, specifically in the form of CTE. Thus, instead of showing no signs of neurodegeneration at 100 years of age, exposure to repetitive mild TBI in this individual might now result in signs of neurodegeneration being apparent at 80. Generally, this would not flag a public health issue given that clinical expression of neurodegeneration is relatively common at this advanced age. However, if the same degree of repetitive mild TBI was experienced by someone who was expected to show clinical signs of neurodegeneration at 65, they might now show clinical signs at 45. This is clearly a major concern and would be identified as a potential public health issue. While the biochemical cascade leading to CTE may be initiated in every individual exposed to repetitive mild TBI (Corrigan et al., 2021), whether that individual shows clinical symptoms of neurodegeneration in their lifetime is thus a matter of genetics. This is not to dismiss subsequent environmental factors; alcohol and some drugs are known to upregulate substance P mediated pathways (Khom et al., 2020), which will only exacerbate any existing neurodegenerative cascade.

The challenge is to identify those individuals who are susceptible to the early expression of neurodegeneration, including CTE. Identification of genetic markers of susceptibility would be ideal, although this may be complicated by the fact that multiple genetic factors, and their interaction, may play a role. Alternatively, there are non-invasive imaging methods that are currently

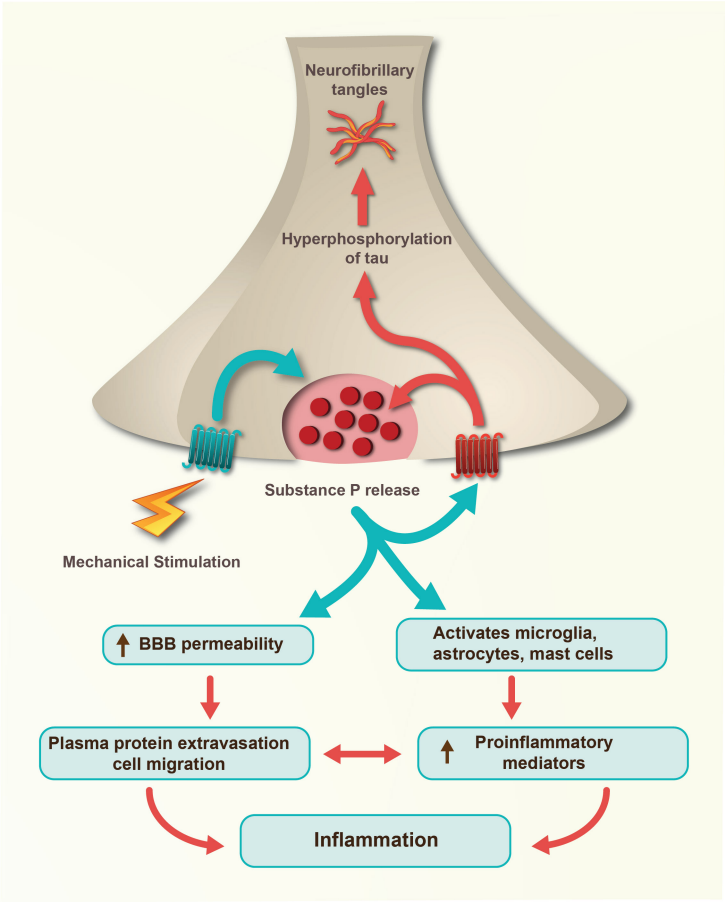

Figure 1 | **Schematic illustrating the link between mechanically stimulated substance P release, tau hyperphosphorylation and neuroinflammation.**
Released substance P binds to its NK1 receptor, which is located on neurons, astrocytes, microglia, mast cells and endothelial cells, to activate kinases associated with tau phosphorylation, as well as initiating and potentiating inflammation. BBB: Blood-brain barrier.

being developed that show particular promise as a means to diagnose CTE in living individuals, although these are still far from being useful for clinical application and prognostication in the early stages of the disease. Similarly, the biomarker field is very active and some results have been very promising. Still, none have been identified that might be used for prognostication. In the absence of surrogate markers of early disease onset and progression, clinical trials of promising interventional therapies, such as SP antagonists for CTE, will be extremely difficult, if not impossible to undertake. Nonetheless, having potential therapies for CTE already in hand is a strong stimulus to invest in the development of future diagnostic technologies, and engenders a sense of great optimism for ultimately controlling this insidious disease. Having genes that increase susceptibility to CTE and triggering its initiation with sports-related repeated concussion may, in future, not carry the concerns that they do today.

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