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Neuroinflammation in ischemic brain injury as an adaptive process

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ABSTRACT

Cerebral ischaemia triggers various physiological processes, some of which have been considered deleterious and others beneficial. These processes have been characterized in one influential model as being part of a transition from injury to repair processes. We argue that another important distinction is between dysregulated and regulated processes. Although intervening in the course of dysregulated processes may be neuroprotective, this is unlikely to be true for regulated processes. This is because from an evolutionary perspective, regulated complex processes that are conserved across many species are likely to be adaptive and provide a survival advantage. We argue that the neuroinflammatory cascade is an adaptive process in this sense, and contrast this with a currently popular theory which we term the maladaptive immune response theory. We review the evidence from clinical and preclinical pharmacology with respect to this theory, and deduced that the evidence is inconclusive at best, and probably falsifies the theory. We argue that this is why there are no anti-inflammatory treatments for cerebral ischaemia, despite 30 years of seemingly promising preclinical results. We therefore propose an opposing theory, which we call the adaptive immune response hypothesis.

Introduction: the case for the maladaptive immune response hypothesis

During and immediately after cerebral ischemic injury a variety of processes combine to create an area of dead cells, an infarction. At the acute stage of injury, reduction in oxygen levels causes disruption in neuronal adenosine triphosphate (ATP) production. This causes the mechanisms which maintain the cell's membrane potential, such as Na^+/K^+ ATPase, to cease functioning, which results in the cell depolarizing and releasing its neurotransmitters, including glutamate [1–3]. Increasing concentrations of glutamate in the extracellular space causes a toxic level of excitation of other neurons, "excitotoxicity". At the same time, reactive oxygen species (ROS) are produced; highly reactive molecules which can react with cellular components, causing more damage [4–6].

These processes cause damage at the "infarct core" over a relatively short period of time. Surrounding the infarct core is the infarct penumbra, an area where brain cells may continue to die for days and weeks in a cascade of secondary "delayed" damage. Inflammation in the penumbra is well established as a contributing factor to continued cell death [7]. Under healthy conditions the brain is an immune privileged organ. But, specialized glia cells called microglia, which act as the resident immune cell for the central nervous system (CNS), are activated by tissue damage [7]. Once activated, microglia secrete pro-inflammatory cytokines which signal to circulating immune cells to infiltrate into the brain [8].

Microglia make up 5–15% of all cells within the CNS [9], where they modulate immune responses [10]. Microglia can sense and respond to changes in the CNS micro-environment using fine processes that extend into surrounding tissue [11,12]. The microglial processes have swellings at the distal ends that are capable of phagocytosis [13]. When microglia recognize foreign particles they become activated. Microglia then modulate the CNS immune response by secretion of cytokines. These cytokines can be anti-inflammatory; for instance, transforming growth factor (TGF)-β1 and interleukin (IL)-10, both of which signal to reduce the activity of immune cells (including microglia) [14–16]. However, the cytokines released by microglial can also be pro-inflammatory; examples include tumor necrosis factor (TNF)-α and IL-1β. These pro-inflammatory mediators induce the expression of adhesion molecules on endothelial cells, which allow leukocytes to attach to the endothelia and migrate across the blood brain barrier (BBB) into the CNS [14–17]. In addition, these cytokines also cause the activation, differentiation and proliferation of leukocytes at the site of injury [14–16]. This process results in inflammation. The increased permeability of the brain vasculature results in swelling of the damaged area and the compounds released by the microglia and leukocytes can combine to create a neurotoxic microenvironment.

It is now clear that microglia are facilitators of immune activity in the CNS, and play a pivotal role in the delayed inflammation induced damage that occurs following acute injuries such as stroke [18–22]. Several histological studies have shown a correlation between the severity of hypoxia ischemia injury in neonatal rats and the level of microglial and leukocyte activation [23,24].

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Furthermore, work by Fan et al. [25] used a rat model of cerebral ischemia to investigate the effect of the inhibition of microglia by minocycline on penumbral damage. Fan et al. [2006] found that microglia inhibition significantly reduced the size of the infarction, suggesting that the activation of microglia is critically involved in penumbral tissue damage. Together this research suggests that neuroinflammation following CNS injury exacerbates the damage and does not aid in survival; we define this as a maladaptive process. As such, inhibiting neuroinflammation at some precise stages in the injury cascade will improve clinical outcomes. We call this the "maladaptive immune response hypothesis".

The problem: why are there no anti-inflammatory treatments for cerebral ischemia in clinical use?

Despite the evidence discussed above, and although the search for anti-inflammatory treatments remains a highly active research program, anti-inflammatory therapies have not been successful in the clinic. In fact, anti-inflammatory treatments have been studied in preclinical research for more than 30 years [26] and yet in that time clinical trials of anti-inflammatories have rarely been found to be effective in human cerebral ischemia or other types of brain injury, and some trials have reported such drugs to have negative effects overall. If inflammation has been known about as a target for so long in preclinical research, why have no anti-inflammatory medicines been incorporated into clinical practice for cerebral ischemia? One possible reason is problems associated with traditional anti-inflammatory agents in cerebral ischemia, such as a lack of specificity and adverse effects. Perhaps when these problems have been solved, new generation anti-inflammatories will prove successful in the clinic. In this article we propose another possible explanation, that the suppression of inflammation is not in fact a rational target for intervention into stroke or other types of cerebral ischemia. We argue that, as neuroinflammation is highly complex and is conserved across many species, it is very likely that it provides a selective advantage, aiding survival and gene transfer to the next generation (i.e., it is an adaptive process). We refer to this notion as the "*adaptive immune response hypothesis*". In the field of CNS injury this hypothesis is counter to the commonly accepted maladaptive immune response hypothesis. However, in the field of peripheral joint injury it is commonly accepted that peripheral inflammation provides a survival advantage through joint immobilization and the signaling of repair mechanisms [27]. Why acute inflammation is accepted as beneficial in the periphery and not in the CNS is normally attributed to the sensitivity of neurons to the chemicals produced by the immune cells and the damaging effects of swelling inside the inflexible skull cavity [7]. However, these ideas do not provide an evolutionary explanation for the existence of neuroinflammation.

The *adaptive* immune response hypothesis; theoretical considerations

Lo [28] propose a schema for the pathological processes that progress after stroke containing several key processes – including excitotoxicity, oxidative and nitrosative stress, and activation of matrix metalloproteinases [MMPs] – where there occurs a biphasic response to intervention; treatments targeting a particular process may be beneficial at one time point, but harmful at an earlier or later point. To explain this Lo [28] introduced the concept of the transition from injury processes to repair processes after a stroke. Lo suggested that signals from some types of injury processes were necessary for the induction of later repair processes.

Lo and colleagues have also discussed the role of inflammation after stroke as a biphasic process [28,29]; early stages of inflammation contribute to the growth of the ischemic lesion and later processes are involved in repair (along with other processes such as angiogenesis). However, we argue that another important distinction is between dysregulated and regulated processes in pathogenesis. Dysregulated processes are those which are normally well-adapted physiological processes, but which are disrupted following cerebral injury and become an exacerbating factor in the pathology. An example is the glutamate signaling system which following injury becomes dysregulated and results in seizures and excitotoxicity. Other processes can be characterized as regulated processes in the pathogenesis, such as the inflammatory response, which is a signaled response that is controlled by both pro and anti-inflammatory cytokines.

Some biphasic responses may be explained in terms of shifts from a state of dysregulation to regulation. For example, neuronal excitation initially exacerbates injury through excitotoxicity but in the later stages of injury appears to be necessary for neuronal repair processes. In addition, some processes may only appear dysregulated, but are in fact are an adaptive and regulated response to injury. Distinguishing between regulated and dysregulated responses is important when considering the pathophysiology of cerebral ischemic injury from an evolutionary perspective. Complex regulated processes must have developed through the process providing a selective adaptive advantage (except in some cases, such as where adaptive evolution lags behind environmental changes, as outlined below). Dysregulated processes represent a breakdown in some adaptive process that may be an unavoidable feature of injury, such as the disruption of ATP synthesis following cerebral ischemia. Reasoning in this way we argue that it is not sufficient to simply target any process involved in the injury phase whilst avoiding interference with the repair phase; it is also important to distinguish between dysregulated and regulated processes even within the injury phase. Specifically, we propose that the acute inflammation cascade is regulated and therefore most likely adaptive. In this way we explain the failure of anti-inflammatories as a treatment for cerebral ischemia. We therefore argue that the inflammatory response that follows stroke is an adaptive process throughout, and that the currently accepted *maladaptive* immune response hypothesis requires substantial rethinking.

As discussed in the introduction, one contributing factor to brain damage is inflammation induced by cerebral injury, thought to be due to the neurotoxic compounds produced by resident microglia and the invading leukocytes, such as Nitric Oxide (NO) and reactive oxygen species (ROS), as well as by the mechanical pressure caused by edema [30,31]. This maladaptive immune response hypothesis seems to be supported by the success of many classes of drugs that suppress the immune system in animal models of cerebral ischemic insult [32–42] (but, see below). Also in support of the maladaptive immune response hypothesis, heightened levels of inflammatory signaling molecules are observed in stroke patients, and levels of these molecules are strongly correlated with the severity of stroke [43].

Running against this is our hypothesis that because inflammation is a signaled and active physiological response to injury it is not maladaptive and pathological, but adaptive. That is, the complexity and universality of the inflammation cascade strongly suggests that it is an adaptive process throughout all of its phases. In support of this there is growing evidence that the immune response to cerebral ischemic injury is crucial during recovery. Activated microglia and subsequent activation of T cells have been shown to improve the outcome following ischemic or excitotoxic injury. Schori et al. [44] found that intracerebral injections of glutamate were more pathological in WT mice compared to athalamic mouse which lack T cells. T cells have been known to remove glutamate from the extra cellular space [45]. Frenkel et al. [46] showed that introducing activated T-helper cells to mice prior to middle cerebral artery occlusion (MCAO) significantly decreased

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infarction size. Accumulating evidence strongly indicates that neuroinflammation is crucial to the generation, migration and differentiation of new neurons following injury; similarly for the formation of new axons, dendrites and synapses of existing neurons [47]. Sasaki et al. [48] induced a global ischemic insult in mice and then tracked the formation of new neurons in the hippocampus. These researchers found that following global hypoxia there was a large increase in the generation and migration of new neurons to the site of damage in the hippocampus. The same researchers also found that inhibiting inflammation by administering different types of COX inhibitors 8 days after the insult significantly reduced the neurogenic response. Further research by Islam et al. [49] demonstrated that IL-6 is a crucial signaling molecule for the differentiation of neuroprogenitor cells into neurons and glia. This suggests very strongly that the immune response following ischemic cerebral insult is crucial to the repair mechanisms of the CNS and that inhibition of this process may have harmful consequences.

Evolution and neuroinflammation; both adaptive and maladaptive hypotheses are consistent with current understanding of evolution

There is evidence that neuroinflammation involves a signaling system that is over 500 million years old [50]. On its own this suggests that acute inflammation that progresses toward a resolution is an orchestrated procedure that is well adapted to a set of tasks, such that intervention with the process is unlikely to be beneficial. On the other hand, it has been suggested that human brains are different from other (particularly smaller) animals brains, and that an evolutionary time lag [51] is responsible for imperfect adaptation of neuroinflammatory processes to the *human* brain (which has evolved very rapidly in a relatively short period of time) [52]. An evolutionary time lag occurs when a selection pressure has changed so rapidly that the allele frequency and composition has not yet stabilized at its most adaptive state. In this case the human brain has changed so quickly that a truly adaptive neuroinflammatory response has not yet evolved. Interestingly, if this time lag exists this would mean that preclinical experiments for anti-inflammatory therapies using animal models for cerebral ischemia would be irrelevant for humans; considering the continual translational failures, this largely appears to be the case. This theory also highlights the important principle that Darwinian selection leads to good *but not perfect* biological functioning. Dawkins [51] discusses at length various "constraints on perfection" such as evolutionary time lags, historical constraints, available genetic variation, and physiological trade-offs (amongst others). Therefore, it may be that although inflammation is an adaptive process, it is an imperfect one and, thus could be improved by human manipulation. Hence, future scientists may find subtle ways to manipulate the inflammatory cascade to promote improved outcomes. But this does not mean that suppressing the inflammatory response *as a whole* at any point in the cascade will be beneficial. Below we critically discuss arguments that have been put forward in support of the theory that the inflammatory response to brain injury is *so imperfect* that it should be considered in large part maladaptive.

Constraints due to scale of injury – is neuroinflammation maladaptive in large brain injuries?

Chronic inflammation is thought as pathological and seemingly maladaptive in comparison to acute inflammation. Could a similar distinction apply to spatial as well as temporal scale? That is to say, is it possible that the immune response to brain damage is beneficial in minor injuries but is pathological for major injuries? The reasoning behind this hypothesis is that although repair processes minor injuries would be subject to natural selection, this might not be the case for major injuries which could leave the individual dead, incapacitated, or at least incapable of reproduction. For example, mammals are unable to regenerate limbs, unlike some amphibians – presumably because any such process would be too slow to save the animal from death given the pace of mammalian life, and hence not subject to adaptive selection.

This theory is difficult to assess for brain injury using the animal model literature, due to the fact that small ischemic insults are not often used in animal models of cerebral ischemic insult [53]. This is because animal models aim to create a large signal to noise ratio, with the signal being the infarction volume, and the noise being the error in measuring the infarction (along with the intrinsic variability of the infarction itself) [53]. Although, this problem is being addressed with advances in the way lesions are induced and measured [53], it is still difficult to compare the effects of anti-inflammatories on small lesions compared with small lesions [54]. However, some studies are suggestive; Ooboshi et al. [33] used both thrombotic stroke and dual carotid ligation to model focal stroke and global hypoxia in rats. Using these two methods Ooboshi et al. [33] found that neuronal loss was less in animals that had been transfected with the anti-inflammatory cytokine IL-10, and the transfection was done after the ischemic insult using a virus vector of gene transfer. This was equally effective in both models. Therefore, as these two methods of ischemic insult represent the two extremes of brain damage, these results do not support the hypothesis that the immune response is beneficial for small brain injury but pathological in a large injury.

Constraints due to evolutionary time lags

Selection pressures are constantly changing, so biological processes can never be perfectly adapted to current conditions [51]. When selection pressures change very rapidly an evolutionary time lag can occur, where the biological processes in question are clearly not optimal for current conditions. For example, the relative difficulty humans have in giving birth has been explained in this way; the selection pressure for larger more complicated brains has changed very rapidly resulting in humans having very large heads relative to body size [55]. This has been proposed to have resulted in the biological processes and anatomy involved in human birth being in a state of evolutionary time lag, where the birth canal is more appropriately sized and adapted earlier in hominid evolution [55]. Therefore, another possible defense of the maladaptive immune response theory argues that the immune response was highly adaptive in ancestral animals but that as the human brain rapidly evolved to become larger and more complex, evolution of the immune system's response has lagged, so that it is currently maladaptive for injuries of CNS but not for injuries to other tissues.

Some evidence in support of this theory can be found in the difference in the way rodents recover from head injury compared to humans. Following an ischemic insult that damages a huge percentage of the cortex a rodent may still function close to normally and swim, walk and eat. A comparative injury in the human would at least be highly detrimental to higher and lower functions of the brain hugely effecting both motor and cognitive function, or more likely it would be fatal. This suggests that the human brain has evolved in such a way that it is now more sensitive to neurological injury than other mammals.

Although this argument for the maladaptive immune response theory has some evidence that is consistent with it, there have been no direct tests of the hypothesis, and can only be considered to be highly speculative at present. Indeed, the presence of an evolutionary time lag would seem to be very difficult to directly address with experimentation, and to assess it indirectly would

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seem to require a much greater amount of knowledge from comparative physiology than is currently available for neuroinflammation.

Constraints due to age-dependent selection

Before reproductive maturity, any biological processes are under the strict control of selection pressures and evolution. However, genes that have beneficial effects in the reproductive period and before may have deleterious effects later in life, after procreation has been successful and offspring have been raised. This theory of senescence predicts that physiological systems may lose efficiency and even become pathological with increasing age at no cost in terms of genetic transfer to the next generation [56]. A relevant example of this is wound repair in young animals, which is much more efficient and less likely to scar than wound repair in the old [57,58]. Therefore the CNS immune response may be adaptive in the young but not in the later stages of life when it becomes maladaptive. If this hypothesis is true the adult models of ischemic cerebral insult like MCAO could be treated with anti-inflammatory agents more successfully than would be the case for models of childhood stroke and hypoxia. This theory cannot be conclusively ruled out, as there are very few published studies that have showed neuroprotection using specific anti-inflammatory agents in young animal models. In fact one study found that there was no protective effect from reducing inflammation in perinatal ischemia [59]. On the other hand, immune suppression may be beneficial in some adult animal models of cerebral ischemia [60–62]. Therefore, evidence for or against this version of the maladaptive immune response theory is suggestive, but still inconclusive.

Adaptive or maladaptive immune response? The pre-clinical evidence

The adaptive immune response hypothesis would be decisively falsified if it could be shown that an agent that *specifically* inhibits the inflammatory response were to be shown to be therapeutic in treating cerebral ischemia in clinical trials. However, common anti-inflammatories have effects on systems other than inflammation, some of which may be neuroprotective in the acute phase of injury. In these cases, if the anti-inflammatory agent were to be shown to be beneficial *specifically in the delayed phase of injury* and the agents non-inflammatory effects only affected the acute stage of injury, then this would also falsify the adaptive immune response hypothesis.

The preclinical evidence appears *prima facie* to support the theory that immunosuppressants are beneficial following ischemic injury (i.e., the maladaptive immune response hypothesis). Many preclinical studies have appeared to show that pharmacologically suppressing the immune response to cerebral ischemic injury is beneficial [32–38,40–42]. However, other types of study have cast doubt on the maladaptive immune response hypothesis. One such study by Clark et al. (2000) showed that mice that lacked the gene for the key inflammatory cytokine IL-6 had similar injuries to control mice in an MCAO model of stroke. This study showed that the KO mice not only lacked IL-6, but also that they produced other pro-inflammatory markers such as TNFα and IL1β at 50% lower levels than the wild type mice after MCAO [63]. These findings are strong evidence against the theory that immunosuppression could reduce brain damage after cerebral ischemia. However, similar studies with KO mice have found pro-inflammatory mediators exacerbate brain damage following stroke [64]. This may be explained by some kinds of immune cells serving a protective role following ischemia whereas others are pathological [44,65–69].

Steroids immunosuppressants as neuroprotective agents

There is some preclinical evidence that steroids are neuroprotective under some circumstances. Corticosteroids such as corticosterone have a strong immune suppressing effect and are so effective in suppressing the immune system they are the most commonly used drug for treating autoimmune disease [70]. However, there is only very weak evidence from preclinical experiments for any benefit from the use of corticosteroids in ischemic cerebral. A study by Tuor et al. [71] used a hypoxia–ischemia (HI) model to show that pre-administration with a corticosteroid drug lowered the level of neurological damage by 90% when compared to the vehicle control group. However, the corticosteroid was only effective when administered before the ischemic insult, but not when administered directly after or 3 h after hypoxia [71]. Given that substantial immune cell infiltration is not seen in the first few hours following the injury and leukocyte numbers reach their peak 72 h after MCAO, it is questionable whether the mechanism of protection was by suppression of the immune response after the initial injury [72]. Tuor et al. [71] proposed that hyperglycemia caused by the corticosteroid may be neuroprotective, itself an idea in conflict with the evidence that insulin is protective following ischemic insult [73].

Goericke et al. [35] investigated the effects of intrathecal administration of corticosteroids in a rat model of stroke. Using this route of administration should increase the anti-inflammatory effects in the brain but without causing hyperglycemia. This approach was neuroprotective up to 30 min after injury in an MCAO rat model of stroke. However, before this can be considered to be evidence in the support of the maladaptive immune response theory, it should be noted that glucocorticoids have direct effects on neurons which include decreased glutamate release, increased GABA release, and decreased Ca^{2+} influx, all of which maybe neuroprotective through anti-excitotoxic mechanisms, i.e., independent of any immunosuppression action [74]. Furthermore, glucocorticoid treatment has failed to progress to clinical success; the Cochrane database lists 8 trials involving 466 people, none of which demonstrated any positive effects in adult stroke [75]. Therefore, glucocorticoids may be neuroprotective through mechanisms other than immunosuppression in animal models, and not be neuroprotective at all in human trials.

Also highly relevant is the CRASH study [76]. Acute brain trauma has similar pathophysiology to cerebral ischemia, characterized by excitotoxicity, oxidative stress and neuroinflammation. Immunosuppressants have been used clinically since the early 1970s, but were not assessed in double blinded placebo controlled clinical trials until 1999 when this trial assessed the effects of the steroid immunosuppressant methylprednisolone in a trial 10,008 with people randomly assigned to the drug treatment group or a placebo group [76]. At the time there were anecdotal reports that many doctors were so sure in the efficacy of immunosuppressants in treating head trauma, they considered this trial to be unethical [77]. However, once the results were collated from the 45 countries involved there was very little doubt that the steroid immunosuppressant increased the fatality rates of the head trauma patients, with mortality rates of 21.5% in the control group and 24.9% in the methylprednisolone treatment group [76,77].

COX inhibitors as neuroprotectants

Non-steroidal anti-inflammatory Drugs (NSAIDS) are the second major class of classical anti-inflammatory agents. Cyclooxygenase (COX) enzymes control the production of prostanoids which are pro-inflammatory signaling molecules. Inhibitors of COX enzymes, NSAIDs, have been found in preclinical experiments to be protective in excitotoxic and ischemic conditions [37,80].

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However, COX enzymes are found in both perinatal oligodendrocytes and neurons and, therefore, the protective effects of NSAIDS may be due to direct action on brain cells rather than through their anti-inflammatory properties. The non-specific actions of various NSAIDs include inhibition of both neuronal NF-κB and adenosine receptors, which could have direct effects on the gene expression and neuronal depolarization, respectively. Also, AM404 metabolite of the atypical NSAID paracetamol (acetaminophen) has effects on the endocannabinoid system, with potentially direct effects on excitotoxicity [78].

Moreover, the prostanoid sub-group prostaglandins cause hyperthermia. Therefore, reducing the production prostaglandins with COX inhibitors would prevent hyperthermia and may induce mild hypothermia. Both classical NSAIDs and paracetamol have well known antipyretic properties. Hypothermia is the only clinically used treatment that has been shown to reduce brain damage after perinatal hypoxia, and hyperthermia is a well-known risk factor for seizures, as well as increasing the metabolic (hence, oxygen) demands. To summarize this section, NSAIDs may be neuroprotective through diverse mechanisms that are partly or wholly independent of their anti-inflammatory properties. Therefore, the success of NSAIDs at reducing brain damage in some preclinical experiments cannot be considered as strong evidence for the maladaptive immune response hypothesis.

Non-classical immunosuppressants as neuroprotectants

Tetracycline antibiotics such as minocycline have been found to have immune suppressing effects. Compounds of this family have been found to be neuroprotective in many ischemic models [22,25,40,79–81]. However, evidence is also building that this group of compounds has a direct action on neuronal apoptosis [82,83]. Tang et al. [84] used cultured neurons that were treated with two kinds of toxins to show that minocycline protected the cultured neurons from death through restoring the expression of the antioxidative thioredoxin-1, and the anti-apoptotic protein Bcl-2. Therefore, it is possible that the neuroprotective effects of tetracycline are independent of their immunosuppression effects [40,85].

Cannabinoid CB2 receptor agonists have been shown to suppress immune cell activation and migration, and to be neuroprotective in a number of animal models, including hypoxia ischemia and stroke [86,87]. However, studies that have shown that CB2 agonists are neuroprotective following ischemic injury have also shown that they may work through non-immune modulating mechanisms. One possible mechanism is via non-specific activation of the cannabinoid CB1 receptor, which may result in a reduction of excitotoxicity Gifford et al. [88].

Neuroinflammation requires an active response by microglia – the CNS specific immune cells involving changes in morphology, gene expression and cell cycle. By contrast, excitotoxicity is a direct consequence of injury, and is usually actively suppressed through adaptive regulatory mechanisms that cause desensitization of neurons. In other words, the damaging aspects of neuroinflammation are a product of adaptive natural selection, whereas the damaging effects of excitotoxicity result from a *breakdown* of adaptive mechanisms. On this basis we argue that excitotoxicity is rational target of pharmacological intervention in a way that immune suppression is not.

Some cannabinoids have also been found to have antioxidant properties [89]. Hampson et al. [90] showed that phytocannabinoids including THC and cannabidiol had a greater antioxidant capacity than α-tocopherol (vitamin E), which is similar to cannabinoids in its lipophilicity, and ascorbate (vitamin C). Following cerebral ischemia, free radical production causes neuronal death in a process that is similar to excitotoxicity, i.e., it is the result of a breakdown of adaptive mechanisms that under normal circumstances regulated levels of free radicals. To repeat the earlier argument, antioxidants would seem to help restore and aid an adaptive regulatory mechanism, whereas anti-inflammatory agents would seem to inhibit an complex adaptation [50].

CB2 receptor activation has also been implicated in increasing insulin secretion and reducing blood glucose levels [91]. High blood glucose levels have been associated with worse outcomes in ischemic cerebral insult [73]. Many cannabinoids also act on a range of other receptors; for example, vanilloid receptors [92–96]. TRPV1 activation has a number of effects on the body; including the induction of hypothermia and vasodilation, both of which are important for neuroprotection [97,98]. It should be noted, however, that work with cannabinoid receptor knock-out mice by Zarruk et al. [99] appears to conclusively demonstrate the specific role of CB2 activation in the treatment of stroke in mice [99]. Nevertheless, there is also some evidence that CB2 agonists have vasodilatory effects independently of TRPV1 [93,100,101]. Supporting this, CB2 agonists appear to have been most effective for occlusion based cerebral ischemic injury models [87,99]. In addition, Zhang et al. [102] argued that CB2 agonists prevent leukocytes from adhering to the endothelia in small blood vessels and in doing so decrease the restriction of blood flow caused by leukocyte adhesion.

Assessing the evidence

The preclinical and clinical trial evidence has not falsified the adaptive immune response hypothesis; i.e., there has been no neuroprotective effect for any pharmacological agent in the delayed stage of damage that can be specifically attributed to an anti-inflammatory action. The immunosuppressing agents that have been tried have a variety of other effects that may explain any neuroprotective action that they might have. However, it is also possible that these agents are not viable neuroprotectants at all; given the failure of agents that have been promising in preclinical research to translate to the clinic it is possible that the preclinical research has been in some way flawed. Supporting this conclusion, studies that have used animals that lack specific genes that involved in the immune response have shown that these animals exhibit similar levels of brain damage after an ischemic insult as control animals, however conflicting evidence also exists [64]. Others have shown that some components of the immune system have beneficial effects following ischemic cerebral insult. Furthermore, studies that have investigated the repair mechanisms of the brain after injury seem to show that the immune response is crucial in signaling the generation and differentiation of new neurons. From this it could be concluded that the maladaptive immune response hypothesis is incorrect or at best only partially correct. We propose this as an explanation why although anti-inflammatory treatments have been studied preclinical research for more than 30 years, they have not been found effective in the clinic [103].

Conclusions & implications

We argue that there is little evidence from preclinical experiments and only weak arguments from evolutionary theory to support the *maladaptive* immune response hypothesis. Therefore, we propose that the *adaptive* immune response hypothesis requires more serious attention. Although highly testable, the adaptive immune response hypothesis has survived conclusive falsification after thirty years of experimental testing. We argue that neuroinflammation is fundamentally different from the type of injury processes that involve a breakdown of otherwise regulated systems, such as glutamate transmission and free radical production.

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Whereas the latter are maladaptive failures of adaptive systems, neuroinflammation is an adaptive process initiated by the injury itself.

If the immune response to injury is not maladaptive it is possible that interfering with it could be harmful. There are at least two ways that this could be the case. First, by disrupting an adaptive injury response, repair processes may be thwarted or delayed, exacerbating injury (as was indeed seen in clinical trials for steroids, see above]. Second, infection is a leading cause of death following a CNS injury. Infection is particularly problematic after brain damage because it can result in an immunosuppressive state throughout the entire immune system, due to an increase in stress hormone levels and increased sympathetic tone. This causes a substantial loss of functional T cell activity [104]. Therefore pharmacological immunosuppression after brain injury might carry a risk of serious side-effects. This is not to deny that *chronic* inflammatory disorders, such as rheumatoid arthritis, may very well involve a dysregulation of some processes involved in inflammation, and hence be maladaptive. But, this itself presumes the adaptiveness of the acute inflammatory cascade following injury in an otherwise healthy individual, and what we question is whether acute neuroinflammation that proceeds to resolution is at any point maladaptive and could reward intervention.

Our hypothesis is highly relevant to the difficulties that have been faced in attempts to translate promising strategies for neuroprotection from preclinical research to the clinic; no neuroprotective agent has yet been found to be effective in human clinical trials [105]. With respect to anti-inflammatory treatments, we suggest that this could be due to a fundamental error in the underlying theory. If true, then this is similar to the situation in several related field; classical and non-classical anti-inflammatories have been completely unsuccessful at treating sepsis in clinical trials despite substantial evidence for therapeutic effects in animal models [106,107]. Similarly, neuroinflammation in the spinal cord is a very well characterized process in animal models of neuropathic pain [108,109] but immunosuppressant drugs do not reduce neuropathic pain in humans (Paul Rolan, pers comm]. Furthermore, a similar evolutionary perspective should be applied to other apparent apparently maladaptive responses to injury; for example gliosis inhibits neurite growth and this is seen as detrimental to recovery [110], however, perhaps this inhibition is preventing the formation of disruptive circuitry in the ipsilateral hemisphere [111].

Conflict of interest

The authors do not have any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work to disclose.

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