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Peripheral inflammation and neurodegeneration; a potential for therapeutic intervention in Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS)

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Abstract

Background: Degeneration of the central nervous system (CNS), also known as neurodegeneration, describes an age-associated progressive loss of the structure and function of neuronal materials, leading to functional and mental impairments.

Main body: Neuroinflammation contributes to the continuous worsening of neurodegenerative states which are characterised by functional and mental impairments due to the progressive loss of the structure and function of neuronal materials. Some of the most common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Whilst neuroinflammation is a key contributor to the progression of such disease states, it is not the single cause as there are multiple factors which contribute. Theoretically, non-steroidal anti-inflammatory drugs (NSAIDs) have potential to target neuroinflammation to reduce the severity of disease states. Whilst some animal models investigating the effects of NSAIDs on the risk of neurodegenerative diseases have shown a beneficial effect, this is not always the case and a large number of clinical trials have not shown the same finding.

Conclusion: Further investigation using more advanced research methods is required to better understand neuroinflammatory pathways and understand if there is still a potential window for NSAID efficacy.

Keywords: Neuroinflammation, Neurodegeneration, Intervention

Introduction

Degeneration of the central nervous system (CNS), also known as neurodegeneration, describes an age-associated progressive loss of the structure and function of neuronal materials, leading to functional and mental impairments [1]. Neurodegeneration is a feature of many incurable and, eventually, debilitating neurodegenerative diseases [2]. As the population's life expectancy continues to rise and the size of the aging population, subsequently, steadily increases [3], the threat of neurodegenerative diseases continues to worsen. For example, between the years 1960 and 2010, the life expectancy at birth in the EU had risen by an astounding 11 years [4]. Some of the most common neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS).

Over the years, a growing understanding of the mechanisms underlying the pathophysiology of such

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disorders has shown continual improvement. The development of experimental model systems which recapitulate characteristic hallmarks of these neurodegenerative disorders has significantly aided such a progression of insight, including the use of yeast, fruit flies, nematode worms and, more commonly, particularly recently, mice [5–9]. More recent advancements have capacitated the ability to produce induced pluripotent stem cells (iPSCs) from differentiated human cells to generate human models of these diseases through the production of patient-specific cell lines in a tissue culture dish [10]. Furthermore, in recent years, these cells have also been cultured in three dimensions, for the first time, producing organoids which represent human tissues including the brain [11, 12]. As these advancements continue to progress, the held understanding of these states follows.

It is now accepted that neuroinflammation, inflammation within the brain or spinal cord, contributes greatly to the overall process of neurodegeneration. Inflammation is the first line of defence of an organism in response to an initial insult, so neuroinflammation is an inherent mechanism which has the purpose of protecting and re-establishing the normal structure and function of the brain, by aiding the recovery of injured neurons, such as in response to infection [13]. Following an infection or inflammatory condition, peripheral immune activation causes the innate immune response to signal to the brain and upregulate cytokine production by the CNS [14]. Whilst the intended purpose of neuroinflammation is beneficial through seeking to overcome the potential threat, if the magnitude or duration of the inflammation is too large or prolonged, respectively, then this process will take a different course. Chronic inflammation has deleterious effects and exacerbates the degree of neurodegenerative states [15].

Although it is believed to be a significant contributor of the most common neurodegenerative diseases, controversy lies in the extent to which peripheral inflammation may be considered a cause of the fatality of neurodegenerative disorders. Gaining a clearer understanding of this will elucidate whether therapeutic intervention involving inhibition of this process may be an effective means of reversing disease progression or, at least, slowing it. The remainder of this review will consider the extent to which peripheral inflammation contributes to neurodegeneration and may be considered a cause of these diseases, in addition to potential therapeutic avenues which have been, or are beginning to be, considered. In order to explore this, AD, PD and ALS will be considered as representations of neurodegenerative states.

Main text

There are several factors which may induce inflammation in the CNS including bacterial infections, viral infections or neuroimmune conditions [16]. Neuroinflammation is an expected feature of the ordinary aging brain although the process is hastened in neurodegenerative states [17]. An acute inflammatory response of the CNS is caused by an immediate activation of glial cells in response to noxious stimuli. When this response is sustained, it leads, ultimately, to neurodegeneration as the blood–brain barrier (BBB) becomes disrupted, allowing an influx of inflammatory cells along with other products with properties that may cause tissue destruction. Elevated levels of inflammatory cytokines in the serum and CNS are also found. In the CNS, proinflammatory cytokines are produced by microglia and astrocytes, the residential immune cells of the CNS which are key to the regulation of brain homeostasis all the way from development, through to adulthood and even aging [18].

Figures 1, 2 and 3 depict this innate immune response.

Astrocytes are the most abundant glial cells of the CNS, comprising around 25% of the cerebral volume and are the first cells that CNS-infiltrating immune cells encounter. Microglia comprise around 10% of the entire CNS population, with the function of constantly surveying the microenvironment and producing factors to influence the surrounding astrocytes and neurons. Moreover, in response to pathogen invasion or tissue

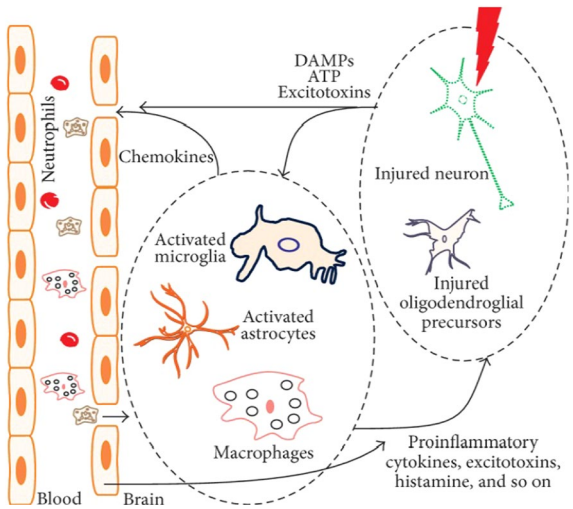

Fig. 1 A schematic depicting the innate response to brain injury. Damage-associated molecular patterns (DAMPs) are sensed by microglia, astrocytes and macrophages causing an increased permeability of the BBB enabling immune cell migration to the sites of tissue damage where inflammatory processes begin to occur through the release of inflammatory mediators. Adapted from Banjara and Ghost [95]

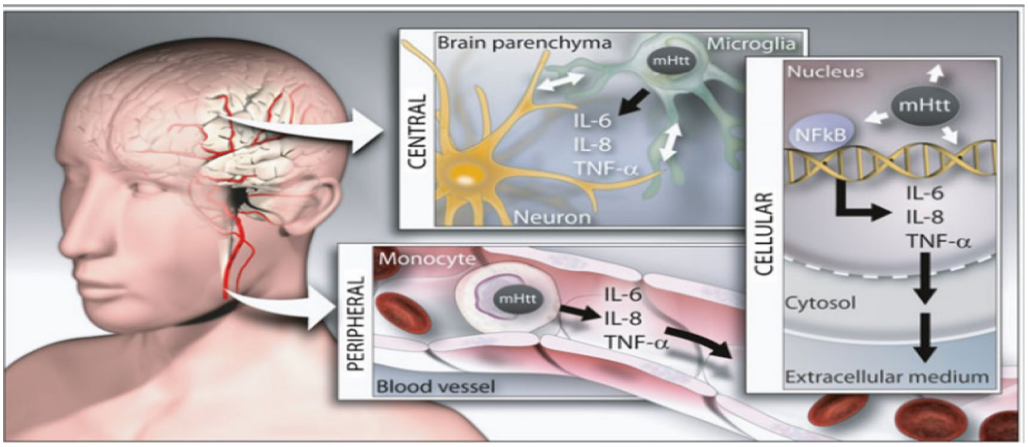

Fig. 2 A schematic depicting peripheral and central immune dysfunction in neurodegeneration caused by cell-intrinsic expression of mHTT and its effects on cellular processes. Adapted from Träger and Tabrizi [96]

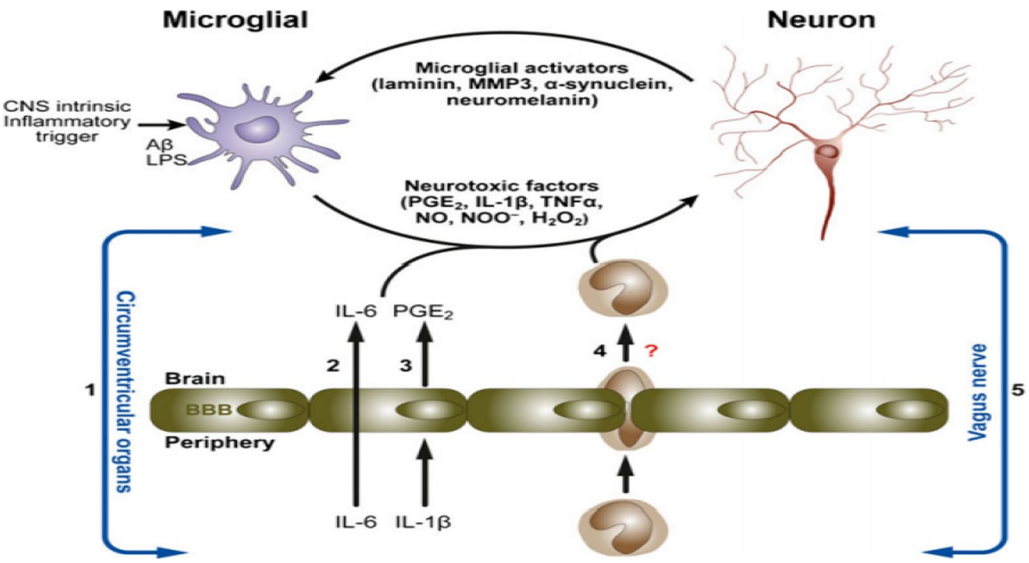

Fig. 3 A schematic depicting routes by which the peripheral immune activation influences neurodegeneration. (1) Mediators of peripheral inflammation and cells are permeable to the brain through circumventricular organs deficient of BBB. (2) Some selected immune mediators, like IL-6, are transported actively across the BBB. (3) Also immune mediators such as IL-1β can result to brain endothelium activation, thereby secreting nitric oxide, cytokines and immunological mediators into the brain. (4) Peripheral immune cells penetrate the brain either directly via the BBB, through the CSF (choroid plexus), thus contributing neurodegeneration. However, it is still unclear the extent to which cells can cross the BBB in neurodegeneration. (5) Finally, peripheral inflammation is translated into the brain through the vagus nerve in the neural reflex which coordinates systemic inflammation by sensing and inhibiting pro-inflammatory markers. Adapted from Träger and Tabrizi [96]

damage, microglia switch from an inactive (ramified) to an activated (amoeboid) state which promotes an inflammatory response in order to initiate tissue repair [19, 20]. However, the persistence of inflammatory stimuli or failure of normal resolution mechanisms leads to inflammation which occurs in tissue pathology and results in the production of neurotoxic factors which further amplify diseases' states [21, 22]. Such neurotoxic mediators converge, functionally, to facilitate mechanisms associated with protein degradation, mitochondrial dysfunction, defective axonal transport and apoptosis. These intracellular mechanisms are associated with the pathogenesis of neurodegenerative diseases, such as AD, PD and ALS [1, 15, 23].

The immune response of the CNS is closely controlled in relation to the periphery [15], so an offense causes

the release of proinflammatory mediators and this leads to permeabilisation of the BBB. Leukocytes, including T cells and macrophages, which share many functional features with microglia, from the periphery are then able to infiltrate the BBB to reach the CNS [24]. The consequence of this is neuroinflammation. When this response of neuroinflammation is merely acute, such that it is of a reasonable magnitude and limited duration, the effects can be beneficial as potential injury will be minimised through activation of innate immunity. On the other hand, when this is prolonged chronically, a sustained release of inflammatory mediators causes an enhanced degree of oxidative and nitrosative stress which perpetuates the inflammatory cycle and contributes to the progression of neurodegenerative diseases [25, 26].

Neurodegenerative diseases

The most common neurodegenerative diseases are characterised by the pathological accumulation of insoluble filamentous aggregates of normally soluble proteins within the CNS.

A summary of these is given in Table 1.

Alzheimer's disease

Alzheimer's disease is the most common type of dementia with approximately over 46 million individuals affected worldwide [27] and an expectation that AD will affect around 115.4 million people by 2050 [28]. A progressive decline of cognition, function and behaviour characterises AD with the corresponding symptoms of memory loss, cognitive impairment and unusual behavioural patterns [29]. Underlying this degenerative process is the production of amyloid beta (Aβ) plaques, which are clumps of insoluble peptides formed from the abnormal cleavage of amyloid precursor protein (APP), as well as neurofibrillary tangles (NFTs) formed by the abnormal phosphorylation of Tau protein [30].

In the case of AD, neuroinflammation can be considered part of a characteristic pathological triad involving Aβ plaques and NFTs, with plenty of evidence of an inflammatory response occurring in AD. For example, transgenic mice expressing a Swedish mutation of the APP gene were produced and successfully expressed features of AD pathology, including extensive extracellular Aβ accumulation and neuritic dysfunction. Immunohistochemical analyses then revealed that activated microglia were located in close proximity to the Aβ plaques in addition to a significantly greater production and release of interleukin-1β (IL-1β) and tumour necrosis factor α(TNF- α), two major proinflammatory cytokines, in comparison with such levels associated with inactive microglia [31]. Prior to this study, there was a lack of suitable animal models to support the direct contribution of inflammatory responses to AD pathology. The group was also built on from previous work by avoiding the use of Griffonia simplicifolia GS B4 Isolectin for detection of microglia [32], as it detects both ramified and amoeboid microglia and, instead, using antibodies to CD45 (leukocyte common antigen) and to class I or II major histocompatibility (MHC) antigens, which merely detect activated microglia [33]. Their key findings coincide with those of other studies [34] including in human post-mortem tissue from AD brains [35]. Furthermore, IL-1β pellet implantation in rats has been shown to promote microtubule activation, p38 mitogen-activated protein kinase (MAPK)-mediated hyperphosphorylation of Tau protein as well as a further increase in levels of its own expression [36]. Other studies have shown microglia located in close proximity to Aβ plaques as staining positively for IL-1β in addition to interleukin 6 (IL-6), TNF-α and monocyte chemoattractant protein 1 (MCP-1) [37], which contributes to astrocyte recruitment around plaques [38].

This evidence alludes to a pathway underlying AD aetiology whereby chronic induction of neuronal injury, due to the presence of Aβ plaques and NFTs, generates a self-propagating cycle involving continually rising IL-1β levels. Such injury triggers microglia and astrocytes to become active, through toll-like receptors (TLR) and receptor for advanced glycation end (RAGE)-dependent pathways [39, 40]. Microglia release TNF- α and IL-1β which can also activate astrocytes, and, similarly, astrocyte activation induces further microglial activation [41]. Activation of microglia causes their migration to the plaques to perform phagocytosis; whilst this effect has a protective purpose, when this is prolonged microglia

Table 1 Common neurodegenerative diseases and characteristic proteins

Disease	Microscopic lesion	Location	Aggregated protein
Alzheimer's disease	Amyloid plaque	Extracellular	Amyloid-β
	Neurofibrillary tangle	Intracytoplasmic (neurons)	Tau
	Lewy bodies (in Lewy body variant)	Intracytoplasmic (neurons)	α-synuclein
Amyotrophic lateral sclerosis	Hyaline inclusions	Intracytoplasmic (neurons)	Superoxide dismutase 1
Parkinson's disease	Lewy bodies	Intracytoplasmic (neurons)	α-synuclein

are no longer able to appropriately process Aβ [42, 43]. Instead, microglial activation will be sustained in a feed-forward loop, or microgliosis, resulting in further accumulation of Aβ, production of inflammatory amplifiers and subsequent sustained proinflammatory cytokine signalling, thus exacerbating AD pathology due to the uncontrollable neuronal damage [44, 45]. Effective therapeutic interference of this invasive cycle may serve as a means of slowing down the progression of AD.

Parkinson's disease

As the second most common neurodegenerative disease, Parkinson's disease is believed to affect 1–2% of the population aged over 60 years of age [46]. PD results from a preferential loss of dopaminergic neurons of the nigrostriatal pathway, resulting in symptoms of motor impairment including the classical resting tremor, limb rigidity, bradykinesia and postural and gait impairments. The degeneration seen in PD becomes more widespread as the disease progression continues, thus implicating more brain regions [47]. Underlying the pathology of PD are Lewy bodies, which are intra-neuronal cytoplasmic inclusion bodies constituted predominantly of α-synuclein [48, 49].

Similar to AD pathology, peripheral inflammation causing neuroinflammation is involved in the pathology of PD [50]. Highlighting this is the common finding of several studies of an increased proportion of active microglia in the substantia nigra of PD patients, post-mortem [51, 52]. In addition to this, elevated levels of inflammatory amplifiers, such as IL-1β, IL-6 and TNF- α, in both transgenic mice which overexpress α-synuclein and in PD patients, in comparison with wild-type levels and otherwise healthy controls, respectively, were found [53–55]. These inflammatory mediators, such as TNF-α, released by activated microglia, disrupt BBB integrity to allow immune cells, macrophages and leukocytes, to enter into the CNS, eventually leading to neuroinflammation [56].

This shows that although neuroinflammation may not be the primary cause of PD, since these findings were observed at symptomatic stages, various models of PD have produced consistent findings, suggesting that neuroinflammation is a crucial contributor to PD progression. Whilst it is clear that microglia and astrocyte activation, via mediators released by injured dopaminergic neurons, is involved, additional in vivo experiments are required for a deeper understanding of the mechanisms underlying this. Such additional insight may aid further development of effective therapeutic strategies which are able to specifically and temporally target inflammatory processes without compromising the potential benefits, such as tissue restoration.

Amyotrophic lateral sclerosis

Another neurodegenerative disease is ALS, which involves progressive deterioration of upper motor neurons (MNs) of the corticospinal tract and lower MNs of the brain stem and ventral roots of the spinal cord, leading to paralysis which, in many cases, is fatal [57, 58]. This process tends to initiate in limbs or bulbar muscles and over time spreads to other regions, eventually resulting in respiratory muscle dysfunction and a consequential respiratory failure. Death usually follows within 2 to 5 years following ALS diagnoses [59]. With no cure, ALS has proven a challenge to treat, as like other neurodegenerative diseases, with only one drug, riluzole, being approved by the Food and Drug Administration as a treatment; however, the mere capacity of this drug is to extend the individual's life expectancy by approximately 3 months, an effect not nearly profound [60, 61].

Whilst the precise pathogenic mechanisms of ALS remain elusive, pathways which involve oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation and protein aggregation are believed to comprise a multifactorial nature of ALS [62]. In many cases, ALS roots largely from mutations of superoxide dismutase 1 (SOD1), although other proteins also contribute [63].

There exists a plethora of evidence for the involvement of neuroinflammation in ALS, including the most common observation of increased microglial activation from cerebrospinal fluid analysis and post-mortem spinal cord samples from ALS patients [64–66], as well as elevated levels of molecules which amplify inflammation, including Interleukin-8 (IL-8) [67], TNF- α, IL-1β, IL-6 and vascular endothelial growth factor [68]. Furthermore, in a transgenic mouse with SOD1 mutations which exhibited ALS-like characteristics, during the course of symptom progression an increased expression of cyclooxygenase type 2 (COX-2) was detected [17]. COX-2 is an enzyme which plays a role in the synthesis of prostanoids, potent inflammatory mediators, particularly prostaglandin E2 (PGE_2) [69]. This was regionally specific; for example, it was seen in the spinal cord but not the cerebellum. Such specificity was not due to an insertional consequence of the transgene, and this is known because the group ensured widespread expression of the mutation. This observation was made in the mice at both early stages of symptom development and also at end stages, in addition to human post-mortem spinal cord samples from ALS patients [70]. The findings of this study highlight a specific role of COX-2 upregulation in neuroinflammation contributing largely to ALS disease progression.

The evidence confirms that neuroinflammation is highly implicated in the motor neuron degeneration seen in ALS, such that signs of neuroinflammation are not only seen in cases where the characteristic symptoms of

ALS have already developed, but also during presymptomatic phases of ALS [71]. Therefore, unlike in AD and PD where neuroinflammation seems a consequence of the initial injury underlying the disorders, neuroinflammation acts as both an initiating and propelling factor in the pathogenesis of ALS. However, it is believed that there is a convergence of factors which lead to the onset of ALS, so further research is required to identify the extent to which neuroinflammation, alone, may serve as a trigger for other factors which contribute [72].

Potential for therapeutic intervention

There are currently no cures for neurodegenerative diseases, and treatment options are limited, in terms of options available, efficacy and merely alleviating symptoms rather that underlying causes [73]. Research has enabled a progressively growing understanding on the involvement of peripheral inflammation leading to neuroinflammation, propelling the degeneration underlying AD, PD and ALS, an area with potential for therapeutic intervention. Such therapeutic strategies would be beneficial by targeting these inflammatory processes, perhaps from the earliest stage possible, without restricting the intended protective effects of inflammation, as an innate immune action of the body in response to the initial tissue injury.

Of particular interest as a treatment avenue for AD have been non-steroidal anti-inflammatory drugs (NSAIDs). Experimental models initially suggested that this might be promising. For example, in transgenic mice overexpressing APP, administration of ibuprofen, a non-specific COX inhibitor, at the stage of amyloid plaque formation, caused a decrease in the level of glial activation and plaque density [74, 75]. Another NSAID, indomethacin, was found to attenuate microglial activation and restore impairment of hippocampal long-term potentiation, the primary underlying process of memory loss, thus alleviating the associated memory deficits upon direct Aβ injections into rat dentate gyri [76].

Despite the promising nature of such findings, the success rates of clinical trials do not correspond with this. In several double-blind, randomised, placebo-controlled trials using nonselective NSAIDS, including ibuprofen and indomethacin, as well as those using specific COX-2 inhibitors, no signs of cognitive impairment amelioration were observed [77–82]. This was even the case when NSAID treatment was maintained for 4 years [83]. This suggests that NSAID treatment is ineffective once the pathology of AD has already taken its course; however, NSAID administration at early stages of Aβ plaque formation may prevent or reduce the impact of the beneficial aspects of neuroinflammation and this would be counterproductive. On the other hand, when NSAID treatment was provided in patients above the age of 65 years with no clinical impairment at the start of the study, age-associated memory decline was attenuated [84]. This suggests a potential window of NSAID efficacy prior to the onset of disease symptoms, during normal aging processes. In order to successfully execute this treatment method, further investigation trials will be required for NSAID as a preventative measure and non-invasive imaging for the detection of amyloid plaques will be crucial for this.

The success rates of NSAIDs in treating PD do not appear to be any more hopeful. A meta-analysis comparing the results of 17 studies, including many which considered long-term NSAID use, comprised of a total of 2,498,258 participants, found no overall association between NSAIDs and the risk of PD [85]. This finding coincides with that of earlier analyses [86]. NSAIDs are not, therefore, accepted as being associated with PD risk reduction [87]. Due to this, along with the, so far, negative results seen with NSAIDs in AD clinical trials and the potential cardiovascular risks discovered in association with particular NSAIDs, it is unlikely that clinical trials for NSAIDs in PD will be considered. Unfortunately, the evidence suggests the same for ALS [88, 89]. Although some subtle differences on the effects of NSAIDs on the relative risk of developing ALS were found between males and females, these differences are of limited significance and were most likely due to chance or an unacknowledged confounder, particularly as this finding is inconsistent with other studies.

As NSAIDs have proven to be unsuccessful in targeting neuroinflammation to alleviate these neurodegenerative states, this warrants the discovery of novel therapeutic interventions which implicate neuroinflammation. For example, polyphenols, including flavonoids, phenolic acids, phenolic alcohols, stilbenes and lignans, such as those found in apples, berries, citrus fruits, broccoli, cocoa, tea and coffee [90], have been found to target toll-like receptor 4 (TLR4) signalling pathways [91]. TLR4 is found on the cell surface of microglia and is involved in neuroinflammatory pathways as it is a first-line host defence receptor against invasive microorganisms, such that loss of function TLR4 mutations have been shown to inhibit microglial activation [92].

However, other studies have shown that loss of function TLR4 mutations do not influence the immune response in neurodegenerative states in humans [93], suggesting in a physiologic situation that other innate immune response receptors may compensate for TLR4 defects. Despite this, the promising nature of other experimental models and repeated propositions that natural compounds targeting TLR4 may act as vital pharmacophores for the development of effective drugs for the treatment of neurological disorders suggests further investigation

should continue. Perhaps, this will require manipulating the TLR4 pathway in a different way or at a more specific and potent stage of disease progression, particularly due to diversity of TLR signalling pathways [94].

Conclusion

Neurodegeneration describes the degeneration of neuronal materials and a subsequent deterioration of CNS function. Inflammation within the CNS, or neuroinflammation, occurs in response to an initial form of tissue injury or damage which varies in different neurodegenerative diseases, such as Aβ plaques and NFTs in AD, α-synuclein forming Lewy bodies in PD and aggregated SOD1 protein in ALS. In neurodegenerative diseases, the purpose of neuroinflammation is to clear up initial infection to ameliorate the severity and progression of the disease; however, when inflammatory stimuli are of too great a magnitude or sustained over a longer period, cytotoxic effects are induced instead due to the persistence of neuroinflammation. The initial injury causes the permeability of the BBB to increase, allowing the migration of activated astrocytes and microglia to the local area and a subsequent release of inflammatory mediators, such as IL-1β, IL-6, IL-8 and TNF- α, thus exacerbating disease states by further facilitating neurodegeneration.

At first glance, targeting neuroinflammatory pathways appears promising as an area for therapeutic intervention, with the expectation that this will slow the disease progression and reduce the severity of symptoms, potentially also lengthening life expectancy. In AD, animal studies exploring the use of NSAIDs produced findings which encouraged further investigation in clinical trials; however, clinical trials were not successful as they showed no link between the use of NSAIDs and risk reduction in AD. In terms of PD and ALS, clinical trials have not been considered due to unsuccessful experimental model trials. Despite this, the notion of partially treating neurodegenerative diseases with NSAIDs is logical and perhaps requires an alternative form of investigation. As mentioned above, three-dimensional models enable realistic analyses of cell-to-cell interactions in physiological situations and in greater depth. As glial cells are highly implicated in neuroinflammatory processes which contribute to neurodegeneration, incorporating neuron–glial interactions into such three-dimensional brain organoid models will aid the elucidation of cell non-autonomous disease mechanisms and may help to yield results which are representative of more accurate human outcomes. This will help a more thorough understanding of precise neuroinflammatory pathways to be obtained and subsequently to clarify whether or not NSAIDs may be still be useful by manipulating neuroinflammatory processes more specifically, such as at precise stages of progression.

Neuroinflammation is a major contributor to neurodegenerative disease progression, although may not be considered a cause in itself as they are typically of a multi-factorial nature. Whilst NSAIDs have not been completely effective in reducing the risk of neurodegenerative disorders in humans, the possibility of this should not be ruled out until advancements in research technologies and processes have been put into action. In the meantime, alternative treatment avenues continue to draw interest for researchers, such as polyphenols which target TLR4 pathways.

Abbreviations

AD: Alzheimer's disease; PD: Parkinson's disease; ALS: Amyotrophic lateral sclerosis; CNS: Central nervous system; iPSCs: Induced pluripotent stem cells; BBB: Blood–brain barrier; AB: Amyloid beta; APP: Amyloid precursor protein; NFTs: Neurofibrillary tangles; IL-1B: Interleukin-1B; TNF-a: Tumour necrosis factor a; CD: Cluster of differentiation; MHC: Major histocompatibility complex; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein; TLR: Toll-like receptor; RAGE: Receptor for advanced glycation end; MNs: Motor neurons; COX-2: Cyclooxygenase type 2; PGE2: Prostaglandin E2; SOD1: Superoxide dismutase 1; IL-8: Interleukin 8; IL-6: Interleukin 6; NSAID: Non-steroidal anti-inflammatory drugs; TLR4: Toll-like receptor 4.

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LH contributed to conception and design of the work. EP was involved in drafting the work, as well as designed the work. CI designed, drafted and revised the work. EM designed as well as revised the work. GI was involved in drafting of the work as well as revision. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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