



Microglial activation and neuroinflammation in Alzheimer's disease: a critical examination of recent history

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The neurofibrillary degeneration that occurs in Alzheimer's disease (AD) is thought to be the result of a chronic and damaging neuroinflammatory response mediated by neurotoxic substances produced by activated microglial cells. This neuroinflammation hypothesis of AD pathogenesis has led to numerous clinical trials with anti-inflammatory drugs, none of which have shown clear benefits for slowing or preventing disease onset and progression. In this paper, I make the point that AD is not an inflammatory condition, and reconstruct the sequence of events during the 1980s and 1990s that I believe led to the development of this faulty theory.

Keywords: major histocompatibility complex antigens, cytokines, amyloid, aging, chronic inflammation

INTRODUCTION

One might reasonably argue that a microglial renaissance occurred during the mid-to late 1980s. Although anatomists of the early 20th century, such as Nissl and del Rio Hortega, had already made seminal contributions toward understanding microglial biology, for reasons unknown microglia remained largely hidden away from mainstream neuroscience for much of the decades following these early studies. During the 1970s and well into the 1980s the one key issue dominating microglial neurobiology concerned their embryological origin, i.e., whether the cells are of mesodermal or neuroectodermal origin (Theele and Streit, 1993). Many would now consider this question resolved in favor of a mesodermal lineage, but rapid developments in the field of neural precursor cells may once again bring the ontogeny issue to the forefront for reconsideration.

The rebirth of microglia in the 1980s occurred because of two major developments: methods for culturing microglial cells *in vitro* and reagents for visualizing cells *in situ* became available. These advances were critical for stimulating renewed interest in the almost forgotten "third element" of Cajal as is abundantly evident now, some 20 years later, by the explosion of published papers on microglial cells. However, excitement over the rediscovery of microglia also produced a major misconception regarding functional roles of activated microglia, namely, that microglial activation is harmful to neurons in the CNS. Thus, with regard to the question posed in this special issue: where did we get lost, the short answer is, we got lost early on by misinterpreting biological functions of microglia. The purpose of this paper is to describe how this misconception came about and how it became entangled with the concept of detrimental neuroinflammation which is now believed by many to underlie not only Alzheimer's disease (AD) pathogenesis but a number of other major neurodegenerative conditions, including Parkinson's disease, amyotrophic lateral sclerosis and HIV-associated dementia.

CONCEPTUAL ERRORS IN THE INTERPRETATION OF MICROGLIAL ACTIVATION

The initial understanding of what constitutes an activated microglial cell was simple and straightforward – activated microglia were identified as reactive mononuclear elements responding to acute CNS injury *in vivo* (Oehmichen and Huber, 1976). These experiments represented a modern day extension of classic experiments performed by Metchnikoff in the late 1800s in that they were focused on studying the inflammatory response, only this time in the brain. There was little doubt that activated microglia were part of an acute cellular response to an injurious stimulus, which for Oehmichen and Huber consisted of implanting glass cover slips into the rabbit brain. A more sophisticated paradigm of eliciting microglial activation whose origins date back to the work of Nissl at the turn of the 20th century, and advocated by Kreutzberg and colleagues beginning in the 1960s was the facial nerve axotomy paradigm. In this model, an acute and local neuroinflammatory response (microglial activation) can be induced in the facial nucleus simply by cutting the peripheral axons of cranial nerve VII. Although Kreutzberg and colleagues did not use the term "inflammation" but usually spoke of microglial activation, it was implicit because microglial activation represents a cellular reaction to injury, which in essence constitutes the definition of inflammation according to textbooks of pathology. Importantly, axotomy-induced microglial activation is associated both temporally and spatially with the successful regeneration of axotomized motoneurons, providing an unambiguous association between microglial activation and the natural wound healing response, and clearly supporting a beneficial role for activated microglia.

The concept of microglial activation changed in the 1980s when researchers began to model it *in vitro*. Pioneering work done by Giulian and Baker (1986) established a relatively simple procedure for isolating and maintaining microglial cells in the culture dish, and their method quickly became the procedure of choice

for many other laboratories interested in studying the biological functions of microglia. In their initial as well as in subsequent papers, Giulian and colleagues emphasized the production of a prototypical proinflammatory cytokine, interleukin-1 (IL-1), by amoeboid microglia (so-called because of their resemblance to macrophages), which was reaffirmed by Hetier et al. (1988) just a couple of years later by showing that IL-1 mRNA synthesis was induced in these cultured cells following their stimulation with bacterial lipopolysaccharide (LPS). With this introduction to neurobiology of LPS-mediated macrophage activation, already well-established and accepted in immunology circles, the flood gates were opened for studying microglial activation *in vitro*. Countless studies have since then been performed using various modifications of the LPS model as well as other immunostimulatory paradigms for studying activated microglia *in vitro*. However, most of these studies have not taken into consideration the fact that microglia activated by LPS *in vitro* behave very differently than microglia activated by injured neurons in the brain. We have previously discussed this discrepancy between *in vivo* and *in vitro* concepts of microglial activation (Streit et al., 1999), pointing out that the generation of microglial cell cultures involves extreme brain damage (chopping and trituration of dissected tissues) inevitably causing immediate activation of microglia and their transformation into brain macrophages. When these activated microglia-derived brain macrophages are additionally stimulated with LPS, the result is superactivated cells that produce not only copious quantities of IL-1 but many other secretory products. It seems that cells treated in this manner are activated to a maximal extent and are near the breaking point; indeed more recent work shows that LPS-mediated overactivation leads to microglial cell death (Liu et al., 2001). Thus, one key juncture where we got lost was in the silent assumption that cultured microglia unstimulated by LPS were representative of resting microglia in the normal brain, and that LPS-activated cells were analogous to activated microglia in the damaged brain. Any extrapolations made from such *in vitro* data are therefore unlikely to apply to most *in vivo* scenarios of microglial activation with the possible exception of a bacterial CNS infection. Case in point, amoeboid microglia *in vivo* do not produce IL-1 (Hurley et al., 1999), as suggested by *in vitro* studies (Giulian et al., 1986). Moreover, the *in vitro* findings on microglial IL-1 production likely caused many to assume that whenever activated microglia were present *in situ* the cells produced IL-1 in a sustained manner. However, IL-1 production *in vivo* varies substantially and even in cases of severe CNS damage, such as spinal cord trauma, the duration of IL-1 production is limited to the first 24 h post-injury after which it drops to control levels (Streit et al., 1998). During the acute neuroinflammatory reaction in response to facial nerve axotomy IL-1 mRNA levels are very low and essentially the same as in uninjured control tissues (Streit et al., 1998). In addition to IL-1, which is often thought of as a potentially harmful cytokine associated with chronic inflammatory states, such as rheumatoid arthritis, other potentially damaging substances were found to be produced by activated microglia *in vitro*. Perhaps most notable and influential in this regard was the early study by Colton and Gilbert (1987) showing that microglia activated by zymosan can produce superoxide anions. Although the authors at the time presented their findings in the context of a bactericidal action of

activated microglia, the data were extrapolated later on by many others to support the idea that activated microglia contribute to oxidative stress in the injured and diseased brain. While *in vitro* studies continued to gain momentum and eventually produced a picture of microglia as neurotoxic effector cells (Boje and Arora, 1992; Chao et al., 1992; Giulian et al., 1993), other researchers were studying microglial activation in a variety of *in vivo* brain injury paradigms, as well as in the diseased human brain, taking advantage of the availability of new antibodies that allowed the visualization of microglia *in situ*.

Soon after the introduction of *in vitro* methods, McGeer et al. (1987) reported in a landmark paper the presence of reactive (activated) microglia in the brains of humans with AD. Their study together with another one by Rogers et al. (1988) 1 year later, and the *in vitro* data showing production of potentially harmful substances by activated microglia would set the stage for development of the notion that detrimental neuroinflammation plays a major role in AD pathogenesis. McGeer's discovery was made possible by the availability of antibodies directed against major histocompatibility complex (MHC) antigens, which are well-known recognition molecules essential for mediating specific cell-cell interaction in the immune system, most significantly antigen presentation. Their findings were spectacular because of a prevailing view at the time that the brain is immunologically quiescent, i.e., an immunologically privileged organ where lymphatic drainage and MHC antigen expression are absent. However, McGeer's identification of activated microglia by virtue of the fact that these cells were expressing MHC class II molecules was not entirely correct because MHC II expression occurs prominently also on non-activated microglia and perivascular cells in the normal human and animal brain (Craggs and Webster, 1985; Hayes et al., 1987; Streit et al., 1989). Nonetheless, the notion that MHC II expression can serve as an objective biomolecular marker for activated microglia was seemingly corroborated by subsequent animal studies that showed increases in MHC II expression on a subset of microglial cells following experimental lesions (Akiyama et al., 1988; Streit et al., 1989; Smetanka et al., 1990), encouraging its widespread acceptance. The idea that neuroinflammatory processes are involved in AD was buttressed further by additional findings from the McGeer group showing presence of complement proteins and integrins in the AD brain (McGeer et al., 1989; Akiyama and McGeer, 1990), as well as by findings showing presence of IL-1 immunoreactive microglia in Down's and AD cases (Griffin et al., 1989). Pretty soon, a large number of other inflammatory mediators, including many cytokines, were being added to the list of substances thought to be consistently increased in the AD brain and by the time a major review on AD and neuroinflammation was published in 2000 (Akiyama et al., 2000), the notion was firmly embedded in mainstream thinking. A potential problem with all of these studies focused on measuring various inflammatory molecules in the AD brain is that most if not all of the inflammatory proteins (similar to MHC antigens) are also expressed in non-AD brains, and that levels of these are likely to vary substantially in both populations depending on whether or not peripheral infections are present. Thus, any future work along these lines should exclude subjects with infectious comorbidities.

ACUTE VERSUS CHRONIC INFLAMMATION AND THE ROLE OF AMYLOID- β PROTEIN

Another place where we got lost was by not differentiating between acute and chronic inflammation and distinguishing between a wound healing response and autoimmune disease, although I will maintain that neither contributes to AD neurodegeneration. While acute inflammation comprises the immediate and early reaction to an injurious event and is basically an adaptive response that paves the way for repair of the damaged site, chronic inflammation results from injurious stimuli that are persistent. There is no evidence of any injurious event in AD that would precipitate an inflammatory reaction, although some might argue that amyloid- β protein (A β) qualifies in this regard (see below). In the periphery, both acute and chronic inflammation are characterized by leukocytic exudates consisting primarily of polymorphonuclear cells (neutrophils) in the former, and mononuclear cells (macrophages, lymphocytes, plasma cells) in the latter. In the CNS, because of the presence of the blood brain barrier, leukocytic exudates may or may not be part of acute neuroinflammation, the facial nerve axotomy paradigm being a premier example of this (Raivich et al., 1998). The classic example of chronic neuroinflammation occurring in the CNS is found in multiple sclerosis, a disease marked by prominent leukocytic infiltrates. While the underlying cause(s) of MS have not been identified, it is probably safe to say that the persistent injurious stimulus that accounts for MS neuroinflammation is a myelin-related protein that has escaped self-tolerance and become an autoantigen, which is consistent with how experimental autoimmune encephalomyelitis is induced in animals. With the chronic persistence of a CNS autoantigen there is a persistent accumulation of blood-derived mononuclear leukocytes in the CNS parenchyma, which mirrors the presence of leukocytic exudates in peripheral inflammatory diseases, such as rheumatoid arthritis or polymyositis. It is the persistent presence of extensive leukocytic infiltrates that eventually produces tissue damage. In AD there are no lymphocytic infiltrates to speak of, making it very difficult to maintain that AD is an inflammatory disease. Nonetheless, it was assumed that the ostensible inflammation in AD is of a chronic and therefore detrimental nature because AD is after all an aging-related condition and a number of studies had shown a progressive increase in the expression of MHC class II antigens in the normal aging brain (Rogers et al., 1988; Perry et al., 1993; Ogura et al., 1994; Sheffield and Berman, 1998), suggesting that normal aging is accompanied by inflammation. Also, the word "disease" implicitly carries the notion of chronicity and so it was assumed that whatever inflammatory changes were detected in AD had been there for some time when, in fact, it is impossible to say so from a one-time post-mortem histopathological observation. The idea that microglia are cytotoxic inflammatory cells that contribute towards neurodegeneration in AD was propagated and ostensibly corroborated through additional *in vitro* studies showing that when cultured microglial cells are stimulated with A β peptides they produce molecules which are toxic to cultured neurons (Meda et al., 1995; Giulian et al., 1996; Combs et al., 1999). The conclusion that A β deposits are inflammatory in the AD brain and incite detrimental inflammatory activity was at this point all but inevitable, especially since it seemed to be consistent with numerous prior histopathological descriptions of microglial

aggregations at amyloid plaques. A β peptides had also been shown to be neurotoxic *in vitro* (Yankner et al., 1989), which probably served to encourage this line of reasoning, although in the same year and in the same journal a report appeared describing a neurotrophic effects of A β peptides *in vitro* (Whitson et al., 1989). Conflicting findings like these underscore the potential fallacies associated with *in vitro* experimentation, where outcomes can be influenced profoundly by small variations in any one of a number of experimental parameters. In any event, a key question within the current context is, does the presence of amyloid deposits in AD brain represent a persistent injurious stimulus that incites chronic neuroinflammation? The answer is, probably not, because despite numerous histopathological studies claiming presence of microglial activation around amyloid deposits, a closer look at these allegedly activated cells has revealed that microglia associated with senile (neuritic) plaques more times than not display a dystrophic rather than an activated morphology (Streit et al., 2009). Moreover, the fact that microglia become clustered at senile plaques is by itself not indicative of an inflammatory reaction but instead is more likely to reflect an abnormal cellular reaction triggered by presence of amyloid fibrils. It is known that diffuse, non-fibrillar (early) amyloid deposits, even when extensive, do not elicit microglial changes (Ohgami et al., 1991; Mackenzie et al., 1995; Streit et al., 2009), and thus any microglial changes that have been associated with more advanced amyloid plaques are likely to be the result of altered chemistry of amyloid peptides. In addition, there is *in vivo* evidence showing increased presence of A β and amyloid precursor protein after traumatic head injury (Smith et al., 2003) strongly supporting the view that increased A β production in AD is the result rather than the cause of CNS disturbances. At the same time, it would be a stretch to postulate that extracellular deposition of amyloid peptides in and of itself constitutes an injury.

So, how does one reconcile the many histopathological descriptions of activated microglia in AD with the claim made here that AD is not an inflammatory disease? First, if indeed microglial activation does occur at some point during the evolution of senile plaques, it does not necessarily have to be detrimental and cause AD neurofibrillary degeneration. Neurofibrillary tangles and neuropil threads are not limited to the vicinity of amyloid deposits and they occur during normal aging, as well as in other neurological diseases and in the absence of amyloid. Second, there is a good chance that non-activated (especially dystrophic) microglia were misidentified as activated cells based not only on the false assumption that MHC II expression is an immunological marker for activated cells, but also because of only a superficial assessment of their morphology. In the late 1980s and early 1990s the idea of morphologically abnormal (dystrophic) microglia did not exist and with the excitement over the rediscovery of microglia researchers were quick to identify any non-ramified microglial cell as activated. Lastly, the possibility that microglial activation observable within the AD brain might be the result of infectious disease in the periphery has never been studied systematically; in other words, studies that have assessed neuroinflammation in AD did not make a distinction between AD cases with and without infectious disease comorbidities, which are quite common in AD patients. We know now that peripheral infections in humans are accompanied by prominent microglial activation

(Lemstra et al., 2007; Streit et al., 2009), and it is certainly conceivable that other, less severe complications, such as pneumonia, could influence microglial activation.

CONCLUSIONS

To sum up briefly where we got lost, most significant was the overinterpretation of cell culture data and the indiscriminate extrapolation of microglial cytotoxin production from an artificial *in vitro* environment to the human brain. There was a clear failure to recognize the disparity between microglial activation, as produced *in vitro* through LPS or other immune stimulation,

and microglial activation as it occurs *in vivo*. Related to this was the swift and categorical acceptance of MHC expression as an objective marker for activated microglia *in vivo*. Finally, the assumption was made that any inflammation-like changes reported in AD were indicative of a chronic and therefore detrimental process that was causative in the development of neurodegeneration.

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