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Interleukin-1β in Central Nervous System Injury and Repair

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Summary

Acute inflammation is a self-limiting, complex biological response mounted to combat pathogen invasion, to protect against tissue damage, and to promote tissue repair should it occur. However, unabated inflammation can be deleterious and contribute to injury and pathology. Interleukin-1β (IL-1β), a prototypical "pro-inflammatory" cytokine, is essential to cellular defense and tissue repair in nearly all tissues. With respect to brain, however, studies suggest that IL-1β has pleiotrophic effects. It acts as a neuromodulator in the healthy central nervous system (CNS), has been implicated in the pathogenic processes associated with a number of CNS maladies, but may also provide protection to the injured CNS. Here, we will review the physiological and pathophysiological functions of IL-1β in the central nervous system with regard to synaptic plasticity. With respect to disease, emphasis will be placed on stroke, epilepsy, Parkinson's disease and Alzheimer's disease where the ultimate injurious or reparative effects of IL-1β appear to depend on time, concentration and environmental milieu.

Keywords

Neuroinflammation; Interleukin 1; IL-1; Injury; Protection; Repair; Neurodegeneration; Neurological disease

Interleukin 1 in the CNS

Interleukin-1 is a cytokine released by many cell types that acts in autocrine and/or paracrine fashion, thereby stimulating a variety of signaling pathways [for a more detailed review see (Dunne & O'Neill 2003; O'Neill & Greene 1998; Weber et al 2010)]. Although since expanded, the canonical family members consist of two agonists, IL-1α and IL-1β, an endogenous antagonist, IL-1ra, and two receptors (IL-1RI and IL-1RII) [reviewed in (Dinarello 2009a; Weber et al 2010)]. IL-1R accessory protein (IL-1RAcP), which complexes with IL-1R1 following binding IL-1, is a required receptor partner in signaling (Cullinan et al 1998). All ligands and receptors are expressed in the healthy CNS at low levels (Breder et al 1988; Lechan et al 1990; Molenaar et al 1993), though data on

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distribution of the signaling receptor IL-1RI (Greenfeder et al 1995) suggest that distinct brain regions may depend differentially on the IL-1 system, at least under basal conditions (Ban et al 1991; French et al 1999; Gayle et al 1997). IL-1RII cannot transduce signals due to a short cytoplasmic tail, effectively rendering it a decoy receptor (Colotta et al 1994; McMahan et al 1991). IL-1ra binds to IL-1RI and thereby prevents IL-1 binding and subsequent signal transduction (Dinarello 1998; Dripps et al 1991). Interestingly, proteolytic cleavage of the IL-1RI and RII extracellular domains produces soluble receptors whose binding to IL-1ra and IL-1β, respectively, lead to either an enhanced (sILR1) or diminished (sIL-RII) inflammatory response (Arend et al 1994; Preas et al 1996). The presence of two inhibitors, IL-1ra and IL-1RII (both membrane bound and soluble forms) suggest that this system is tightly controlled for the maintenance of cellular health.

At first viewed as merely a peripheral messenger that communicated with the CNS via passage across the blood brain barrier (Banks & Kastin 1991; Banks et al 1991), IL-1 is now known to be produced directly by cells of the CNS including microglial cells (Giulian et al 1986; Hetier et al 1988; Yao et al 1992), astrocytes (Knerlich et al 1999; Lieberman et al 1989; Zhang et al 2000), oligodendrocytes (Blasi et al 1999), and neurons (Lechan et al 1990; Takao et al 1990; Watt & Hobbs 2000). These same cell types are also capable of responding to the cytokine (Ban et al 1991; Ban et al 1993; Blasi et al 1999; Cunningham & De Souza 1993; French et al 1999; Friedman 2001; Hammond et al 1999; Pinteaux et al 2002; Tomozawa et al 1995; Wang et al 2006; Wong & Licinio 1994). Interestingly, neurons express a novel functional isoform of IL-1RAcP that mediates an alternative signaling pathway (Huang et al 2011). Further, a yet-to-be-identified IL-1 signaling receptor within the CNS has been postulated. Touzani and colleagues report that exogenously administered IL-1β significantly increases cerebral ischemic damage in IL-1RI null mice compared to vehicle-treated control mice, in a manner that could not be obviated by co-administration of IL-1ra (Touzani et al 2002). IL-1β treatment increases the expression of approximately 400 genes in mixed glial cultures derived from IL-1RI-null mice (Andre et al 2006). Finally, outside-out patched membranes from retinal ganglion cells — which lack all intra-cytoplasmic signaling machinery — respond to exogenously applied IL-1β (5 ng/mL for 150 sec) with decreased sodium and potassium currents that could not be reversed by the co-application of IL-1ra (Diem et al 2003). Although these studies suggest that IL-1β can signal in an IL-1RI-independent manner, no identification of this putative, alternative CNS IL-1 signaling receptor has been proffered.

With respect to the two agonists, IL-1α is translated as a 31-kD pro-peptide, although, prior to cleavage, this molecule still has full biological activity; that is, pro-IL-1α initiates signal transduction when bound to its receptor (Mosley et al 1987). Interestingly, IL-1α does not contain a leader sequence, therefore, it cannot be released by the cell via normal Golgi apparatus-mediated vesicular exocytosis. Instead, after translation it remains within the cytoplasm where it becomes myristolated and inserted into the plasma membrane. The majority of pro-IL-1α remains within the cell (Endres et al 1989; Lonnemann et al 1989; Schindler et al 1990); however, upon cell injury/death, it can be released into the extracellular space where cleavage by extracellular proteases can occur. Therefore, the current literature supports the hypothesis that the major function of IL-1α is that of an autocrine growth factor and/or a mediator of local inflammation (Dinarello 1996; 2009a).

Unlike IL-1α, IL-1β has a TATA box within its promoter region in addition to a cAMP responsive element (Shirakawa et al 1993; Tsukada et al 1994), an NF-κB binding site, an AP-1 site and an Sp-1/PU.1 binding site (Shirakawa et al 1993). These transcriptional elements allow for the induction of IL-1β mRNA by a variety of microbial (*e.g.*, lipopolysaccharide [LPS] and teichoic acid) and non-microbial stimuli (*e.g.*, hypoxia, hyperosmolarity, thermal injury and gamma radiation). Translation occurs upon activation of MAP kinases (Lee et al 1994) yielding a 31-kD pro-peptide, pro-IL-1β, which must be cleaved by the cysteine protease caspase-1 (a.k.a. interleukin-1 converting enzyme or ICE) to adopt biological activity (Cerretti et al 1992; Thornberry et al 1992). Like IL-1α, absence of a signaling sequence indicates that a classical pathway of exocytosis is not utilized for IL-1β release. While the exact mechanism by which IL-1β is released from cells is unknown, there is some consensus that — at least from cells of the monocyte/macrophage lineage — IL-1β release is dependent on ATP, its purinergic receptor $P2X_7$ (Bianco et al 2005; Clark et al 2010; Sanz & Di Virgilio 2000; Solle et al 2001), and calcium (Andrei et al 2004; MacKenzie et al 2001). However, while macrophages lacking $P2X_7$ receptors fail to secrete IL-1β following ATP exposure, secretion induced by the K^+ ionophore, nigericin, is not altered in the $P2X_7$-deficient cells indicating the involvement of an additional regulatory pathway(s) (Solle et al 2001). A few major hypotheses have been put forth (Singer et al 1995) (Andrei et al 2004) (MacKenzie et al 2001) (Brough & Rothwell 2007) (Qu et al 2007).

Since most studies to elucidate release mechanism utilize cells of the macrophage lineage, further study in different cell types is warranted (Yazdi et al 2010). To wit: there is evidence that IL-1β can be released exocytotically from neurons (Tringali et al 1996; Tringali et al 1997; Watt & Hobbs 2000). Hypothalamic explant cultures release IL-1β when incubated with high K^+ via a process blocked by tetrodotoxin and voltage-gated Ca^{2+} blockers (ω-conotoxin and verapamil), implicating calcium-dependent exocytosis (Tringali et al 1996; Tringali et al 1997). Loss of IL-1β immunoreactivity from nerve terminals of vasopressin and oxytocin positive neurons within the neurohypophysis upon sustained lactation (facilitating oxytocin release) or a hyperosmotic challenge (facilitating vasopressin release) provides further support for a neuronal release mechanism (Watt & Hobbs 2000). Whether calcium-dependent exocytotic release occurs from neurons from other areas of the brain seems likely, but remains to be experimentally established.

IL-1β in CNS Physiology: Positive or Negative Modulatory Function?

The presence of IL-1RI and IL-1β under basal conditions in the CNS suggests a normal physiologic role for IL-1β. Indeed, IL-1β has important functions in the regulation of core body temperature, which has been extensively studied [for a detailed review see (Dantzer & Kelley 2007; Dinarello 2004)]. Additionally, compelling evidence suggests a physiological role for IL-1β in sleep (De Sarro et al 1997; Imeri & Opp 2009; Krueger et al 2001; Taishi et al 1997). Of particular interest to this review is the neuromodulatory effects of IL-1β on synaptic transmission.

Synaptic Plasticity

The first study to investigate a role for IL-1β in synaptic plasticity did so using a long term potentiation (LTP) paradigm. LTP is defined as a persistent increase in synaptic efficacy and is thought to be a biological correlate to learning and memory (Bliss & Collingridge 1993). Exogenous application of IL-1β substantially reduced the magnitude of long term potentiation (LTP) when applied 20 min prior to tetanic stimulation of the rat mossy fiber path (Katsuki et al 1990). Furthermore, this effect was blocked using the synthetic tripeptide Lys-D-Pro-Thr, a reagent previously shown to antagonize the peripheral hyperalgesic effects of IL-1β (Ferreira et al 1988). Interestingly, the tripeptide alone, which presumably antagonized any endogenous IL-1β released, did not affect LTP acquisition, suggesting that endogenous IL-1 signaling did not contribute to this form of synaptic plasticity under these experimental conditions (Katsuki et al 1990). Although antagonism of LTP in the mossy fiber pathway is highly correlative with amnesia (Satoh et al 1986; Satoh et al 1988), it is not a model of classical Hebbian NMDA-receptor dependent LTP (Harris & Cotman 1986; Zalutsky & Nicoll 1990). Bellinger and colleagues were the first to investigate the effects of IL-1β on this form of LTP (Bellinger et al 1993). IL-1β applied both 10 and 60 min prior to tetanus-induced LTP also significantly attenuated the induction of LTP within the rat Schaffer collateral pathway (Bellinger et al 1993).

Surprisingly, experiments designed to examine the effects of endogenous IL-1β on LTP found opposite results. IL-1β mRNA expression is enhanced one hour after LTP induction in rat hippocampal slices *in vitro* and *in vivo* in the ipsilateral hippocampus of rats that had robust potentiation lasting at least 8 hr (Schneider et al 1998). Blockade of endogenous IL-1β by acute application of recombinant IL-1ra abolishes Schaffer collateral LTP in mouse (Ross et al 2003) and prevents LTP maintenance (but not initiation) in rat (Schneider et al 1998). Additionally, attempts to induce *in vitro* (Schaffer collateral) and *in vivo* (mossy fiber path) LTP in IL-1RI null mice either completely failed or the potentiation was drastically reduced (Avital et al 2003).

These seemingly paradoxical effects of IL-1β are observed in behavioral experiments as well. Mice completely lacking endogenous IL-1 signaling (IL-1RI null mice) demonstrate hippocampus-dependent learning deficits as measured by poorer performance in the Morris water maze (Avital et al 2003), suggesting that endogenous IL-1β is required for normal learning. In support, animals with chronic blockade of IL-1RI signaling in the CNS via transgenic overexpression of human IL-1ra also demonstrate impaired learning (Oprica et al 2005; Spulber et al 2009). Recombinant IL-1β applied either into cerebral ventricles or directly into the hippocampus of normal mice results in the impairment of memory (Barrientos et al 2002; Hein et al 2007; Pugh et al 1999). And finally, animals engineered to overexpress IL-1β chronically in hippocampus also demonstrate impaired spatial and contextual memory development (Matousek et al 2010; Moore et al 2009)

Altogether, these experiments highlight the complexity of IL-1 signaling on experimental LTP and ultimately in learning and memory animal behavioral paradigms. What the data suggest is that physiological levels of IL-1β, presumably released from neurons, function as a neuromodulator to promote experimental LTP and hence memory acquisition and

retention. In contrast, pathophysiological or "inflammatory levels" —in the case of the overexpression studies from astrocytes but also potentially from resident microglial cells or infiltrating myeloid cells — antagonize the synaptic responses associated with LTP leading to failure of memory acquisition or its recall. Indeed, in an elegant study, Goshen and colleagues confirm that intrahippocampal injection of a high concentration of IL-1β or administration of rIL-1ra produce memory deficits, whereas infusion of a low concentration of IL-1β facilitates memory formation in rat (Goshen et al 2007). Interestingly, the hypothesis that an enhanced pro-inflammatory phenotype in brain plays a role in age-related cognitive decline has recently been posited (Viviani & Boraso 2011). Possible mechanisms underlying the plasticity-modulating properties of IL-1β involve its ability to positively and/or negatively regulate voltage- and ligand-gated neuronal ion channel excitability (Gardoni et al 2011; Huang et al 2011; Lynch 1998; Miller et al 1991; Viviani et al 2003; Viviani & Boraso 2011; Wang et al 2000a; Yang et al 2005; Zhang et al 2008; Zhou et al 2011). Overall, the ultimate effect of IL-1β on LTP and associated learning and memory paradigms appear to be cell and target specific, as well as, concentration-dependent.

IL-1β in CNS Pathophysiology: Deleterious or Protective?

IL-1 is rapidly induced in brain tissue following acute brain injury and has been shown to be upregulated in more classical neurodegenerative diseases. The predominate view-point is that IL-1β contributes to and/or sustains the pathophysiological processes. However, studies also point to its potential role in protection and repair. Below, the more complex and contextual actions of IL-1β in the CNS will be discussed.

Seizures and Epilepsy

The hippocampus, a brain structure implicated in the generation of seizures, has been shown to express both IL-1β and IL-1RI (Ban et al 1991; Breder et al 1988; Farrar et al 1987; French et al 1999; Gayle et al 1999; Huitinga et al 2000; Lechan et al 1990; Plata-Salaman et al 2000; Takao et al 1990; Wang et al 2000a). Evidence from several studies suggests that IL-1β may influence acute seizure development and activity and/or epileptogenesis, the process by which the brain becomes prone to spontaneous seizure activity. However, the nature of its role in these processes remains controversial. A comprehensive review has recently appeared (Rijkers et al 2009).

Three single nucleotide polymorphisms (SNP) of the human IL-1β gene have been identified and all involve C-to-T switches (Huynh-Ba et al 2007; Shirts et al 2006; Wang et al 2007). Of the three, the IL-1β -511T polymorphism has been associated with an increased susceptibility to seizures or epilepsy (Kauffman et al 2008) (Kanemoto et al 2000; Kira et al 2005; Ozkara et al 2006). Interestingly, leukocytes taken from patients bearing the -511T haplotype produce less IL-1β following LPS stimulation than those of haplotype -511C (Wen et al 2006). Given the ability of IL-1β to modulate synaptic currents (*vide supra*), it is interesting to speculate that an increased susceptibility to seizures — defined as a transient disturbance of normal cerebral function caused by abnormal neuronal discharges (Victor & Ropper 2002) — might result from a deficit of IL-1β production.

Recent data from our lab supports this supposition. Using transgenic mice harboring targeted deletions in the genes for IL-1β or its signaling receptor, IL-1RI, — which addresses the role of endogenous IL-1β production — we find that the incidence of convulsive seizures induced by the chemoconvulsant pentelyenetetrazol (PTZ) increases in both null mutant mouse lines compared to their respective wild-type littermate controls (Claycomb et al 2012). Hence, the lack of IL-1β signaling reduced PTZ seizure threshold suggesting that IL-1β functions to suppress or dampen neuronal excitability (Claycomb et al 2012). This differs from a previously published study using IL-1R1 null mutant mice, which demonstrated that motor seizures are delayed following intrahippocampal bicculline adminstration with no change in severity or incidence of seizures (Vezzani et al 2000). Moreover, the incidence of seizures induced by intrahippocampal bicuculline injection in mice genetically engineered to overexpress recombinent IL-1ra (rIL-ra) in the CNS was reported to be reduced, supporting a pro-convulsant role for endogenous IL-1β (Vezzani et al 2000). Differences in the chemoconvulsant (bicculline vs. PTZ) and its route of administration (intrahippocampal vs systemic) and the background strain (129/SV vs. C57Bl/6) might explain these discrepant results. However, a higher incidence of sustained generalized convulsive seizure behavior and mortality following systemic kainic acid administration was observed in IL-1β null mice in a B6/B10 background, as compared to their wild-type littermate controls (Claycomb et al 2012), indicating that the potential anti-seizure actions of endogenous IL-1β is neither model nor background specific.

When IL-1β is administered exogenously, most (De Simoni et al 2000; Dube et al 2005; Ravizza et al 2008b; Ravizza et al 2006; Ravizza & Vezzani 2006; Vezzani et al 1999; Vezzani et al 2000; Vezzani et al 2002; Vezzani et al 2004) but not all (Miller et al 1991; Sayyah et al 2005) studies report a pro-convulsive phenotype. Although the reasons for this discrepancy are not immediately evident, differences in experimental paradigms here too exist. For example, the route of administration of convulsant differed. When convulsant stimuli were administered locally into the hippocampus, exogenous IL-1β promoted seizures (De Simoni et al 2000; Vezzani et al 1999; Vezzani et al 2000), whereas it suppressed seizure activity generated when the convulsant was administered systemically (Miller et al 1991). Additionally, intracerebroventricular administration of IL-1β exhibited anti-convulsant actions elicited by electrical stimulation of the amygdala (Sayyah et al 2005) but pro-convulsant properties when electrical seizures were initiated in the hippocampus (De Simoni et al 2000).

The conclusion that IL-1β contributes to the process of epileptogenesis must also be approached with caution. Although levels of IL-1β in the hippocampi and cortex of epileptic EL mice are elevated during the time of presumed epileptogenesis (Murashima et al 2008) and expression of both IL-1β and IL-1RI are up-regulated in the kindled CNS (Plata-Salaman et al 2000), this is merely an association. Given our results, it seems plausible that the increases of endogenous IL-1β and IL-1RI may serve as compensatory response geared toward dampening seizure activity associated with epileptogenesis (Claycomb et al 2012). Indeed, administration of IL-1β antagonized electrical-kindling of the amygdala (Sayyah et al 2005), although pharmacological antagonism of ICE suppressed electrical-kindling of the hippocampus (Ravizza et al 2008).

Overall, available literature with respect to the role of IL-1β in seizure generation and epilepsy formation is contradictory and could potentially be due to the variations in experimental models employed. It is clear that the effects of IL-1β differ when produced endogenously or offered exogenously, vary by brain region, and may even be dependent on the type of convulsant utlized. While no model is perfect, the question as to which, if any, most effectively mimics the human condition is, at present, unanswerable. Thus, testing the validity of the experimental findings via demontration that neutralization of IL-1β signaling provides a positive — and not negative outcome as some data might predict — will only be determined via clinical testing.

Parkinson's Disease

Substantia nigral dopaminergic neuronal cell loss is pathoneumonic of Parkinson's disease (PD). Although the exact causes are not known, the disease is associated with a profound inflammatory reponse evident at the histological level by the presence of microgliosis and astrocytosis. The prevalent view is that inflammatory processes play an important role in pathogenesis of this disease (Tansey et al 2007). Increased IL-1β levels have been detected in the cerebrospinal fluid and in the striatum post-mortem of PD patients (Mogi et al 1994) as compared to control patients and tissues. Single-nucleotide polymorphisms (SNPs) in the IL-1 α and β genes have been reported to be more frequent in some (McGeer et al 2002; Wahner et al 2007) (Nishimura et al 2005; Schulte et al 2002) but not all PD cohorts (Pascale et al 2011) (Moller et al 2004). However, experimental data points to a role for IL-1 in both injury and repair.

In the MPTP mouse model of PD, treatment with minocycline prevents activation of microglia, IL-1β release, and dopaminergic neuronal cell death (Wu et al 2002), suggesting a possible role for IL-1β in neuronal cell death. Supporting this supposition, Ferrari and colleagues report that chronic expression of IL-1β in the rat substantia nigra (using recombiant adenovirus) elicited most of the characteristics of PD, including progressive dopaminergic cell death, akinesia and glial cell activation (Ferrari et al 2006). Taking the opposite approach, and coming to the same conclusion, Klevenyi and colleagues demonstrate that mice deficient in ICE are less susceptible to MPTP toxicity *in vivo* (Klevenyi et al 1999).

In contrast, in the 6-hydroxydopamine (6-OHDA) model of PD, mice deficient in IL-1R1, show a worse disease outcome — defined as lack of dopaminergic neuron sprouting after lesioning — compared to the control cohort, implying that IL-1 imparts a protective role (Parish et al 2002). Remarkably, IL-1RI −/− animals completely lacked microgliosis and astrogliosis, leading the authors to speculate that decreased neuronal sprouting was due to a lack of trophic support from activated glial cells (Parish et al 2002). Indeed, several studies demonstrate that IL-1β-stimulated astrocytes support neuronal survival via production of neurotrophic factors (Albrecht et al 2002; John et al 2005; Saavedra et al 2007). However, others demonstrate that IL-1β can interfere with neurotrophin signaling (Soiampornkul et al 2008; Tong et al 2008). Regardless of the exact mechanims by which this might occur, Parish's study corroborates the results of a much earlier study performed in 6-OHDA lesioned rats (Wang et al 1994). In this study, both histological (tyrosine hydroxylase

immunoreactive (TH-IR) fibers) and behavioral outcomes (amphetamine-induced turning) are improved when IL-1 pellets are implanted directly into the caudate nucleus when compared to placebo-treated animals assessed 8 weeks after the lesion (Wang et al 1994). Hence, in these 6-OHDA studies, IL1-β appears to encourage repair.

Overall, it would appear that the potential mechanims by which IL-1β may influence the development, progression or protection from PD requires further exploration. As it is now accepted for ecosanoids (Serhan et al 2007), and also seems likely for Alzheimer's disease (*vide infra*), it seems plausible that IL-1β may be deterimental early on via contribution to the pathological environmental mileu, but in later stages or when presented in a pharmacological context, could contribute to regeneration and repair. A better understanding of the timing and duration of the inflammatory vs. repair response could be crucial to devising effective neuroprotective therapies for PD.

Alzheimer's Disease

A role for IL-1β in amyloid plaque formation in the AD brain was first postulated by Vandenabeele and colleagues (Vandenabeele & Fiers 1991). Elevated levels of IL-1 were found in post-mortem brain tissue from (Griffin et al 1989), as well as in CSF (Blum-Degen et al 1995; Cacabelos et al 1991) of, Alzheimer's disease patients. Thus the hypothesis that excessive expression of IL-1 in brain might represent the driving force for the cascade of events that culminate in the neuropathological changes characteristic of AD, namely neuritic tangles and amyloid plaques, was borne. Indeed, regional relationships between activated IL-1 positive microglia, tau-positive neuritic tangles, β-amyloid plaques, and activated astrocytes seem to support a causal association (Griffin et al 1995; Sheng et al 1996; Sheng et al 1995; 1998). But is this increase harmful or could it be compensatory and beneficial? Perhaps both. An excellent review describing the evolving perspective on the role of IL-1β in AD has appeared elsewhere (Shaftel et al 2008); hence only highlights are discussed below.

Human IL-1 gene polymorphisms — associated with increased IL-1 production — have been documented to increase the relative risk for AD and/or promote earlier disease onset (Grimaldi et al 2000; Licastro et al 2004; Mrak & Griffin 2000; Nicoll et al 2000). In seeming support, IL-1 can increase expression of β-amyloid precursor protein (βAPP) (Goldgaber et al 1989; Griffin et al 2006; Ma et al 2005; Yang et al 1998b) and has been tied to formation and exacerbation of neurofibrillary tangles as well (Griffin et al 2006; Sheng et al 2000). Interestingly, Aβ can directly activate processes leading to the secretion of mature IL-1β (Halle et al 2008) representing a potential feed forward pro-inflammatory response mechanism. Moreover, mice lacking IL-1ra show enhanced microgliosis and neuronal cell death when human IL-1β is infused into the cerebral ventricles, suggesting that the lack of this negative regulator to the system can increase AD-like pathology (Craft et al 2005). Overall, the initiation and propagation of neuroinflammatory changes in AD have been tied to demonstrable changes in CNS IL-1β levels [for review see (Mrak & Griffin 2005)].

Nevertheless, recent data indicate that the story is more complex. Within the hippocampus, chronic overexpression of IL-1β did indeed trigger a profound neuroinflammatory response (Matousek et al 2012). Yet, surprisingly, AD pathology in a model of Alzheimer's disease

(APP/PS1 transgenic mice) is ameliorated, as measured by a decrease in β-amyloid plaque size and frequency (Shaftel et al 2007). Unlike chronic expression in the substantia nigra (*vide supra*), sustained hippocampal expression of IL-1β produced these potentially protective responses without inducing overt neurodegeneration (Matousek et al 2012), although suppression of adult neurogenesis does occur (Wu et al 2012). Of note, a recent study in an Tg2576/IL-R1 −/− mouse show no clear alterations in β-amyloid deposition when compared to Tg2526 controls (Das et al 2006). Clearly more information is needed to determine whether the timing of the response, the nature of the response stimulus, and the differential cellular processes set in motion may affect the ability of IL-1β to trigger adaptive, reparative responses in the setting of AD.

Cerebral Ischemia (Stroke)

Unlike the other maladies discussed in detail above, there is incontrovertible evidence that supports the conclusion that IL-1β contributes to the evolution of the infarct [for reviews see also (Fogal & Hewett 2008; Loddick et al 1998; Rothwell et al 1997; Rothwell & Luheshi 2000; Rothwell & Relton 1993; Rothwell & Strijbos 1995)]. Establishing a cause-and-effect relationship, administration of either an IL-1β neutralizing antibody (Yamasaki et al 1995) or IL-1ra (pharmacologically or genetically) markedly reduces subsequent cerebral ischemic damage (Betz et al 1995; Loddick & Rothwell 1996; Martin et al 1994; Mulcahy et al 2003; Relton & Rothwell 1992; Yang et al 1998a; Yang et al 1999; Yang et al 1997). Animals deficient in ICE, the enzyme necessary for processing and activation of IL-1β, also show diminished infarct volumes along with a concomitant reduction in IL-1β levels (Hara et al 1997; Liu et al 1999; Schielke et al 1998). Mice lacking the ligand IL-1 (α and β) or the signaling receptor, IL-1R1, have less brain injury after middle cerebral artery occlusion (MCAO) than their wild-type counterparts (Boutin et al 2001; Fogal et al 2007; Ohtaki et al 2003) [but see also (Touzani et al 2002)]. Interestingly, mice null for the IL-1ra gene have larger infarct volumes and increased mortality after experimental cerebral ischemia indicating that this endogenous protective mechamism is triggered following stroke to limit damage (Pinteaux et al 2006). Even intraventricular injection of recombinant IL-1β, while not toxic alone, increases neuronal injury after MCAO in rat (Yamasaki et al 1995). Finally and most importantly, the concentration of IL-1β is significantly increased in the cerebrospinal fluid of stroke patients (Gusev & Skvortsova 2003; Tarkowski et al 1999) and positive results of a prospective Phase II placebo-controlled study of recombinant human (rh)IL-1ra in patients with acute stroke have been published (Emsley et al 2005). Thus, the totality of experimental – and human data – provide compelling evidence that IL-1β is a contributing factor in brain injury that follows cerebral ischemia. While the exact mechanism(s) by which IL-1β mediates these neurodestructive responses following cerebral ischemia are incompletely defined, plausible theories can be found in these comprehensive reviews (Fogal & Hewett 2008; Pinteaux et al 2009).

Although it seems clear cut, we included the discussion of cerebral ischemia here because evidence suggest that the upregulation of IL-1β following ischemic insult may be a part of a protective response that ultimately goes awry. In support of this idea, IL-1 has been demonstrated to be a mediatior of ischemic tolerance (Ohtsuki et al 1996), highlighting its ability to effectively mount protective responses. The preconditioning response to sublethal

global ischemia was blocked by administration of rIL-1ra and mimicked by the addition of either IL-1α or IL-1β (Ohtsuki et al 1996). Further, support for the assertion that IL-1β can promote positive outcomes is shown by the fact that IL-1β can reduce excitotoxic neuronal cell death, a main contributor to ischemic injury. Neuron death induced by the addition of ionotropic glutamate receptor agonists NMDA, AMPA, and kainate in primary neuronal cultures and in organotypic slice is effectively ameliorated with treatment with rather high concentrations of IL-1 (Bernardino et al 2005; Carlson et al 1999; Ohtsuki et al 1996; Pringle et al 2001; Strijbos & Rothwell 1995; Wang et al 2000b). This may be due to its ability to protect neurons and promote growth and/or survival via stimulated production of neurotrophic factors (Carlson et al 1999; Strijbos & Rothwell 1995). However, when paradigms involving energy deprivation — which might more faithfully mimic the *in vivo* situation associated with cerebral ischemia — are employed, IL-1β potentiates neuronal injury (Fogal et al 2005; Jackman et al 2012; Pringle et al 2001).

Why these dichotomous results? Previous work from our lab indicate that IL-1β regulates the expression and activity of a cystine/glutatmate antiporter, system x_c^-, in astrocytes exclusively and that glutamate exported via astrocytic system x_c^- directly underlies the neurotoxic propensity of IL-1β under hypoxic conditions (Fogal et al 2007; Jackman et al 2010) Interestingly, increased activity of system x_c^- is not inherently injurious as under physiological conditions the accumulation of glutamate exported is prevented by its rapid clearance from the extracellular space; consequently, no neuronal toxicity is observed (Fogal et al., 2005). In contrast, when glutamate uptake is impaired, as occurs under hypoxic conditions, increased system x_c^- activity can result in the accumulation of extracellular glutamate and subsequent excitotoxic neuronal cell death (Fogal et al 2007). A previous study reported that neuronal cell death induced by IL-1β required astrocyte activation as well (Thornton et al 2006).

Interestingly, the same transporter fluxing the glutamate which produces excitotoxicity during periods of energy deprivation has a Janus-face and has a well-characterized role in the synthesis of the antioxidant molecule glutathione (Bannai & Tateishi 1986; Meister & Anderson 1983). In this respect, astrocytes function as indispensible support cells by protecting themselves and neurons against oxidative insults (Gegg et al 2005; Jakel et al 2007; Shih et al 2003; Tanaka et al 1999). Hence, it is intriguing to speculate that under conditions of cerebral ischemia, IL-1β is released as a protective mechanism to increase glutathione synthesis in efforts to thwart oxidative stress (Jackman et al 2011).

Conclusion—It is becomingly increasingly clear that IL-1β is important for normal brain function. An equally impressive amount of literature support its role in pathology. Although, anti-IL-1 therapies have proven to be revolutionary treatments for several human autoinflammatory disorders [reviewed in (Dinarello 2009b)], demonstrating a causitive role in these diseases, a clear cause-and-effect relationship between the presence of neuroinflammatory processes and CNS damage does not always exist. Indeed, its pleitrophic effects in the brain indicate that despite having potent pro-inflammatory functions, IL-1β can also participate in neuroprotection, tissue remodeling and repair. So whether IL-1β initiates damage, results from damage and goes on to promote, halt or repair injury may depend heavily on the context, that is, the local concentration, the prevailing environmental mileau,

the cellular target, the presence or absence of negative feedback regulators, and the temporal characteristics of the response. Shaftel and colleagues said it best: “IL-1 can no longer be regarded as simply the villian in the setting of brain injury and disease, but instead must be understood as a factor that can influence the balance between beneficial and detrimental outcomes” (Shaftel et al 2008).

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