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REVIEW ARTICLE

The Role of Glutamate and the Immune System in Organophosphate-induced CNS Damage

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Abstract Organophosphate (OP) poisoning is associated with long-lasting neurological damage, which is attributed mainly to the excessive levels of glutamate caused by the intoxication. Glutamate toxicity, however, is not specific to OP poisoning, and is linked to propagation of damage in both acute and chronic neurodegenerative conditions in the central nervous system (CNS). In addition to acute excitotoxic effects of glutamate, there is now a growing amount of evidence of its intricate immunomodulatory effects in the brain, involving both the innate and the adaptive immune systems. Moreover, it was demonstrated that immunomodulatory treatments, aimed at regulating the interaction between the resident immune cells of the brain (microglia) and the peripheral immune system, can support buffering of excessive levels of glutamate and restoration of the homeostasis. In this review, we will discuss the role of glutamate as an excitotoxic agent in the acute phase of OP poisoning, and the possible functions it may have as both a neuroprotectant and an immunomodulator in the sub-acute and chronic phases of OP poisoning. In addition, we will describe the novel immune-based neuroprotective strategies aimed at counteracting the long-term neurodegenerative effects of glutamate in the CNS.

Keywords Glutamate · Organophosphates · Neuroinflammation · Microglia · Immunomodulation · T cells

Introduction

Organophosphate (OP) poisoning, either accidental or intentional, is still regarded as a major threat to the health of vast populations, both military and civilian (Markel et al. 2008; Sidell et al. 2008). The most devastating impact is expected to occur in chemical warfare or terror scenarios, with projected exposure to high or lethal doses of nerve agents (NAs). Even in cases of transient exposure and despite antidotal treatment, brain damage may occur, associated with long-lasting neurological and psychological injuries (Kadar et al. 1992, 1995; Yanagisawa et al. 2006; Hoffman et al. 2007; Yamasue et al. 2007; Markel et al. 2008; Sidell et al. 2008). Prolonged exposure to low levels of organophosphates may be deleterious as well (Kamel and Hoppin 2004; Golomb 2008; Chao et al. 2010). In OP poisoning, shortly following cholinergic hyperstimulation, other neurotransmitter systems are also activated. Among these, the glutamatergic system is the most pronounced (McDonough and Shih 1997; Raveh et al. 2008; Sidell et al. 2008; Ballough et al. 2008).

Glutamate is the major excitatory neurotransmitter in the brain, and is involved in different activities and pathways in the central nervous system (CNS) and beyond (Ghosh and Greenberg 1995; Danbolt 2001). It is essential for almost all aspects of normal brain function including cognition, memory, and learning (Bliss and Collingridge 1993; Yirmiya and Goshen 2011). However, when in excess, glutamate may be neurotoxic and has a major role in the

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generation and propagation of brain damage in many CNS injuries, either acute, like trauma, intoxication, and infection, or chronic neurodegenerative diseases, like multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) (Coyle and Puttfarcken 1993; Danbolt 2001). Therefore, the glutamatergic system is pivotal for understanding the pathological mechanisms underlying neurodegeneration as well as for developing medical interventions that target more efficiently the secondary long-term effects of CNS damage.

If until recently emphasis was given mainly to the acute excitotoxic effects of glutamate, there is now a growing amount of evidence of its immunomodulatory effects on the brain and the peripheral immune system. Neurodegenerative conditions in the CNS are known to activate microglia—the resident immune cells of the brain. For decades, microglial activation was believed to be destructive in the context of the CNS tissue, contributing to secondary degeneration (Liu et al. 2002; Monje et al. 2003). However, it was demonstrated that if microglia cells are properly activated by T cell-derived cytokines and recruitment of blood-borne monocytes, they can support buffering of excessive levels of glutamate, secrete neurotrophic factors, and support neurogenesis (Shaked et al. 2004; Simard et al. 2006; Ziv et al. 2006; El Khoury et al. 2007; Beers et al. 2008; Butovsky et al. 2006; Chiu et al. 2008; Ekdahl et al. 2009). Some of these protective effects were suggested to be triggered by glutamate itself, via the appropriate receptors, expressed by a variety of cells in and out of the CNS, including astrocytes, microglia, macrophages, T cells, and other peripheral cells and tissues (Schori et al. 2002; Pacheco et al. 2007; Papadia and Hardingham 2007; Juliot-Pieper et al. 2011).

In this manuscript, we will describe the recent evidence concerning the cross talk between glutamate and the immune system in OP poisoning, as well as in other neurodegenerative conditions. In addition, we will discuss the development and adjustment of appropriate medical countermeasures, aimed at counteracting the long-term neurodegenerative effects of glutamate in the CNS.

General Overview of Glutamate in the CNS

Functional Role of Glutamate and Glutamate Receptors: Neuroprotection and Repair

Glutamate activities in the CNS are mediated by two major types of receptors: the ionotropic glutamate receptors (iGluR) and the metabotropic glutamate receptors (mGluR).The iGluR families are ligand-gated ion channels, and include the *N*-methyl-D-aspartate (NMDA), 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propionic acid (AMPA), and Kainate types, and are involved in neuronal plasticity (Ozawa et al. 1998; Traynelis et al. 2010). The mGluRs are G-protein-coupled receptors that signal via GTP-binding proteins and second messenger systems (Ozawa et al. 1998; Traynelis et al. 2010; Niswender and Conn 2010). Glutamate homeostasis is regulated by the high-affinity, Na^+-dependent glutamate transporter systems composed of several types of transporters expressed in various CNS neuronal and glial cells. They mediate clearing of the excess of extracellular glutamate by cellular uptake, which allows terminating the transmission cycle at glutamatergic synapses and preventing toxicity to neurons. The most prominent of these are the excitatory amino acid transporter (EAAT) 1 expressed in astrocytes, and EAAT2, expressed in microglia (Danbolt 2001; Kanai and Hediger 2004). Normally, these transporters are expressed constitutively in astrocytes, which carry out glutamate uptake in the CNS, yet their expression is induced in activated microglia (Gras et al. 2011).

Glutamate activates neuroprotective responses and supports neurogenesis (Pacheco et al. 2007; Whitney et al. 2009). The neuronal response to activation of NMDA receptors (NMDARs) depends on their spatial location. Activation of synaptic NMDARs promotes neuronal survival, while extrasynaptic receptor activation promotes neuronal death and oxidative stress (Papadia and Hardingham 2007). Likewise, signaling via mGluRs in neurons also has either protective or deleterious effects, as there are different receptor types which differ in their signaling mechanisms (Bruno et al. 2001; Byrnes et al. 2009a). Group I mGluR agonists protect neurons by activation of antiapoptotic nuclear factor (NF)-κB pathways, while iGluRs activate the proapoptotic pathways (Bruno et al. 2001; Pizzi et al. 2009).

As mediators in neuronal functioning and survival, glial cells play an important part in protective and beneficial responses to glutamate. Some of these responses are aimed at oxidative stress, like driving cysteine uptake via the X_c^- transporter system and increased glutathione production in astrocytes (Garg et al. 2008; Frade et al. 2008). Activated astrocytes express group I and group II/III mGluRs, mainly mGluR5 and mGluR3 (Biber et al. 1999). Inflammatory and toxic agents or stressors like hypoxia-induced apoptosis, loss of neuronal support functions, and neurotoxicity (Giffard and Swanson 2005), which can be relieved by activation of group II or III mGluR agonists. The beneficial effects of activation of group II mGluRs like mGluR3 in astrocytes are protection from apoptosis (Ciccarelli et al. 2007). This neuroprotective activity is associated with induction of tumor growth factor (TGF)-β and nerve growth factor (NGF) production (Bruno et al. 2001; Corti et al. 2007; D'Antoni et al. 2008), as well as with increase in glutamate uptake (Yao et al. 2005). These and other

responses were studied with pharmacological agonists in the context of drug discovery, but there is evidence that they are mediated by glutamate at physiologically relevant levels (Corti et al. 2007; Romao et al. 2008).

Glutamate Toxicity

Transient elevation in intracellular free calcium is a universal signaling mechanism, and regulator of different intracellular processes, from cell growth and metabolism to cell death, in addition to learning and memory (Carafoli 2002). However, excessive or sustained stimulation by glutamate, through a rise in intracellular Ca^{2+}, leads to mitochondrial dysfunction, accumulation of reactive oxygen species (ROS), and nitrous oxide, and oxidative stress, making the neurons predisposed or hypersensitive to glutamate-mediated damage and leading to excitotoxic neuronal death (Coyle and Puttfarcken 1993; Ghosh and Greenberg 1995; Wang and Qin 2010). The glutamate-induced neuronal death was described as composed of two phases: an initial phase which is characterized by necrosis caused by ROS and nitrogen oxidizing species (NOS), followed by a slower degeneration of the surviving cells, which is mediated by programmed cell death (PCD) signaling (Ancarkrona et al. 1995). The current view of neuronal death due to glutamate, ROS or other cytotoxic agents is as a continuum of cell death mechanisms, starting with apoptosis (or autophagy) at low levels of initial stimuli, going through apoptosis–necrosis hybrid forms, and finally regulated necrosis, in response to the most noxious stimuli, stressing that necrotic death is programmed rather than accidental (Martin 2010). The process of PCD is a composite array of many cellular effects, involving not only the mitochondria but also the endoplasmic reticulum, lysosomes, and cell/organelle membrane transporters, converging to Ca^{2+} homeostasis dysregulation (Wang and Qin 2010; Zündorf and Reiser 2011). Failure of the cysteine–glutamate balance, caused by excess of glutamate at levels that inhibit cystine uptake, may result in neuronal death due to glutathione depletion and oxidative stress in addition to Ca^{2+}-mediated cell death (Reynolds et al. 2007).

The Role of Glutamate in the Acute Phase of OP Poisoning

OPs, and especially NAs, are potent acetylcholinesterase (AChE) inhibitors. Exposure to an OP compound leads to muscarinic, nicotinic, and central effects. The muscarinic effects include miosis, salivation, diaphoresis, rhinorrhea, pulmonary congestion, and the nicotinic effects include muscle tremors deteriorating to muscle paralysis. When casualties are exposed to moderate or high doses of OPs, they may develop long-lasting seizures (Eisenkraft et al. 2007; Marrs 2007; Sidell et al. 2008; Ballough et al. 2008). Furthermore, if left untreated, these seizures progress to status epilepticus (SE) and cause irreversible seizure-related brain damage (McDonough and Shih 1997; Shih et al. 2003; Ballough et al. 2008). The typical neuropathological damage is bilaterally symmetrical, with the most severe damage seen in temporal lobe structures (i.e., piriform and entorhinal cortices, hippocampus, and amygdala) as well as in the thalamus (Kadar et al. 1992, 1995; Zimmer et al. 1997a, b; Baille et al. 2005; Ballough et al. 2008; Collombet 2011). As a result, the prevention of seizures and development of SE following OP poisoning are regarded as a primary objective of medical treatment (Shih et al. 2003; Eisenkraft et al. 2007). This objective becomes increasingly difficult to achieve as time elapses before therapy is started, and seizures become less responsive to medical treatment (Chapman et al. 2006; Eisenkraft et al. 2007; Ballough et al. 2008).

There is strong evidence that by using appropriate antidotal treatment shortly after exposure one can minimize OP's detrimental effects on the brain and save lives (Newmark 2004; Eisenkraft et al. 2007; Weissman and Raveh 2008; Sidell et al. 2008). The mainstay of antidotal treatment includes the use of the anticholinergic drug atropine together with an oxime reactivator (Newmark 2004; Sidell et al. 2008; Ballough et al. 2008). However, though these drugs greatly reduce morbidity and mortality, they do not prevent brain damage and seizure-related brain damage. Currently, benzodiazepines were added to the treatment protocols of casualties having OP-induced seizures and/or convulsions (Eisenkraft et al. 2007; Markel et al. 2008; Sidell et al. 2008; Ballough et al. 2008), yet in some cases this would probably not be enough. Even in cases where appropriate antidotal treatment is given, we sometimes witness long-term sequella consisting of personality changes, sleeping disturbances, and learning and memory deficits of the injured individual (Hoffman et al. 2007; Marrs 2007; Sidell et al. 2008).

When looking at the CNS immediately after OP exposure, inhibition of AChE and increase in synaptic acetylcholine (ACh) levels lead to a burst of excitatory amino acids including glutamate, which stimulates the AMPA and NMDA glutamate receptors (McDonough and Shih 1997; Weissman and Raveh 2008). This neurotransmitter imbalance results in seizures as mentioned earlier. According to McDonough and Shih (1997), the initial events leading to OP-induced seizures can be divided into three phases: an early cholinergic phase, taking place from the start of intoxication up to ~5 min later, followed by a transitional phase, with mixed cholinergic and noncholinergic activity that lasts up to 40 min post-onset, and finally a noncholinergic,

cell damage phase. Studies employing agent and drug microinjection or tissue ablation showed that seizure activity starts at localized regions in the piriform cortex or amygdala and spread to other regions (Zimmer et al. 1997b, 1998; Myhrer et al. 2008; Skovira et al. 2010). The major noncholinergic effects in the development of seizures and in the secondary effects of the seizure activity result from activation of the AMPA and NMDA receptors (McDonough and Shih 1997).

The patterns of neuronal death following intoxication with the NA soman were shown to include several morphological variants, representing mixed features of necrosis, apoptosis, and other forms of PCD (Baille et al. 2005; Collombet 2011). Time course studies of the neuronal fate in the amygdala and hippocampus revealed an initial early phase of neuronal death, followed by prolonged survival of degenerating neurons, which start to die from 15 or 30 days, depending on the brain region, up to 90 days post-intoxication (Collombet 2011). Neuronal regeneration was observed, starting at early time points after intoxication in both hippocampus CA1 region and amygdala, characterized by glial scar formation and angiogenesis (Collombet 2011).

The seizures in soman- or sarin-exposed animals are accompanied by inflammatory processes in the affected brain regions, with a rapid initial activation of microglia and astrocytes (Zimmer et al. 1997b; Collombet 2011; Finkelstein et al. 2012), induction of proinflammatory cytokine expression, mainly tumor necrosis factor (TNF)-α, interleukin (IL)-1α, IL-1β, the anti-inflammatory cytokine IL-6 (Williams et al. 2003; Chapman et al. 2006; Dhote et al. 2007; Johnson and Kan 2010), macrophage inflammatory protein (MIP)-1α, the chemokine (C-X-C motif) ligand (CXCL)-1 (Johnson et al. 2011), cyclooxygenase-2 (Angoa-Perez et al. 2010), and prostaglandin E_2 (Chapman et al. 2006). TNF-α and IL-1β are expressed primarily in activated microglia, while IL-6 is expressed mainly in neurons and hypertrophic astrocytes (Johnson and Kan 2010). CXCL1 is expressed mainly by neurons and endothelial cells, and MIP-1α is expressed by neurons and microglia (Johnson and Kan 2010). Recent genome-wide transcription profiling studies on rat brain regions at various time points after acute exposure to soman and sarin were in agreement with previous studies on expression of early inflammatory markers, and showed that at 24 h following seizure onset, among the most significant functions identified were inflammatory response and signaling pathways including immune cell trafficking (Dillman et al. 2009; Spradling et al. 2011a, b).

The involvement of glutamate in the pathogenesis of OP-induced seizures and subsequent neuronal damage, neuroinflammation, and behavioral deficiencies is evidenced by the superiority of drugs combining anticholinergic and antiglutamatergic effects (e.g., caramiphen or benactyzine) over anticholinergic-only (e.g., scopolamine) or antiglutamatergic-only compounds in prevention of OP-induced brain damage and cognitive impairment (Weissman and Raveh 2008; Raveh et al. 2008). The control of OP-induced seizure activity in animal models by the NMDAR antagonist MK-801 was inconsistent, probably due to timing effects and an inability to dissociate the cholinergic and glutamatergic effects at the early phases of intoxication (McDonough and Shih 1997; Myhrer et al. 2008; Skovira et al. 2010; Deshpande et al. 2010), stressing further the need to engage both of these pharmacological systems in the immediate therapy. However, studies employing NMDAR antagonists like gacyclidine, ketamine, and others together with traditional antidotes were effective in controlling seizures, mitigating neuroinflammation, and brain damage and increasing survival compared to traditional antidotes only (Ballough et al. 2008), thus stressing the importance of the glutamatergic toxicity in secondary degeneration following OP intoxication. Recently, a detailed study of the effects of the anticholinergic–antiglutamatergic drug caramiphen was shown to inhibit behavioral seizures and neuronal degeneration in the sensitive brain regions of soman-intoxicated rats, with reduction of NMDA-induced electrical activity and enhancement of γ-amino-butyric-acid (GABA)-induced electrical activity in brain slices (Figuerido et al. 2011), thus corroborating earlier studies demonstrating the efficacy of caramiphen in neuroprotection from NAs (Weissman and Raveh 2008; Raveh et al. 2008).

The Immune System in Neuroinflammation and Neurodegeneration

In recent years, numerous studies have heightened the key role of the immune system in maintaining the brain and in supporting its plasticity (Ziv and Schwartz 2008; Kokaia et al. 2012; Kyritsis et al. 2012). The classical view of the immune system was in the context of fighting pathogens and removal of foreign elements, with avoidance of recognition and action against the "self", whose breakdown was regarded as a hallmark of autoimmune diseases. Research in the last decade has challenged this view, and today immune recognition of self-components is seen as part of normal physiology, as long as it is properly regulated (Schwartz and Kipnis 2011). In particular, it was demonstrated that the peripheral adaptive immune system is needed to support ongoing hippocampal neurogenesis, spatial learning and memory, and the ability to cope with mental stress (Kipnis et al. 2004c; Cohen et al. 2006; Lewitus and Schwartz 2009). These studies had suggested that the peripheral immune system provides active maintenance of the CNS tissue and ensures proper neuronal functioning by buffering deviations from homeostasis

(Moalem et al. 1999; Hauben et al. 2001; Kipnis et al. 2002; Shaked et al. 2005).

The control of these processes breaks down in pathological conditions—either acute, such as mechanical injury, ischemia, and intoxication, or chronic neurodegenerative diseases like ALS, AD, MS, PD, or some infectious diseases. A hallmark of the pathogenesis in these conditions is inflammation, induced in response to the presence of injured or dying neurons (Jin et al. 2010; Glass et al. 2010). The primary goals of the inflammatory responses are to remove pathogens, cellular debris, and toxins, and make room for tissue regeneration. But as they involve toxic mediators, "innocent bystander" cells may be afflicted and the results may be devastating. In the late stages of acute conditions, the immune networks recover, the inflammation subsides, and tissue regeneration takes place. The recovery is mediated by immune cells, capable of restoring the homeostasis by buffering cytotoxic substances, and supplying neurotrophins and growth factors in support of neurogenesis and neuronal survival (Hohlfeld et al. 2007; Whitney et al. 2009; Schwartz and Shechter 2010). However, the recovery may be incomplete, as in case of scar formation or other long-term remains, like cognitive impairment or chronic epilepsy which appears in some models of neural injury (Vezzani and Granata 2005). In the case of chronic neurodegenerative diseases, the inflammation is uncontrolled and self-propagating (Glass et al. 2010).

The cellular and molecular elements involved in the physiological and pathological processes belong to the innate and the adaptive immune systems. As we shall discuss in the following paragraphs, the same immune elements—cellular and molecular—may have detrimental or beneficial influences. The reasons for these differential effects are not completely known, but it can be stated that the effect is dependent on the context of the physiological environment or timing. As glutamate homeostasis is central in the pathogenesis of these neural injuries, the role of the immune cells and mediators in its control will be emphasized.

Immunomodulatory Function of Microglia and Astrocytes

The major resident innate immune cells in the CNS are the microglia. Under normal conditions, microglia cells exist in an apparently quiescent state termed "resting microglia". This term is a misnomer, as in this state they are active in monitoring the environment of the CNS (Hanisch and Kettenmann 2007; Saijo and Glass 2011). In response to pathological stimuli, such as pathogen invasion or neural damage, microglia transform into "activated microglia", which are different morphologically and functionally, and play an active role in neuroinflammation. The activated state is not a single one but a series of phenotypes, which may be beneficial, or detrimental (Hanisch and Kettenmann 2007). The beneficial functions are phagocytosis of pathogens, cellular debris, and infiltrating neutrophils (Jin et al. 2010), release of neurotrophic substances, sequestration of toxic materials and support of neuron survival, neurogenesis and neuronal migration (Hanisch and Kettenmann 2007; Ziv and Schwartz 2008; Saijo and Glass 2011; Yirmiya and Goshen 2011). However, the toxic products they release may cause collateral damage to neurons (Hanisch and Kettenmann 2007; Saijo and Glass 2011).

Activated microglia display immune functions and phenotypic plasticity similar to activated peripheral macrophages. Like macrophages, microglia express an array of receptors—purinergic and ionotropic glutamate receptors, toll-like receptors (TLRs), and NOD-like receptors (NLRs)—enabling them to detect and respond to signals of pathogen invasion and cellular damage (Saijo and Glass 2011). The microglia also respond to neuronal signals that suppress immune activation in order to maintain homeostasis (Saijo and Glass 2011). In the classical activation phenotype or M1 (Colton 2009), microglia express the macrophage-like functions of antigen presentation, phagocytosis, production of ROS, NOS, proinflammatory cytokines, and glutamate (Schwartz et al. 2003; Takeuchi 2010; Saijo and Glass 2011). When activated by strong proinflammatory agents like lipopolysaccharide (LPS) or amyloid-β peptides, they become highly neurotoxic, but their activation can be modulated to more benign phenotypes (Schwartz et al. 2003, 2006; Colton 2009; Choi et al. 2012). On the other hand, the anti-inflammatory cytokine IL-4, which is produced either locally or by immune cells in the periphery, was shown to direct microglia to a neuroprotective phenotype referred to as alternative activation or M2 (Colton 2009). These microglia do not secrete neurotoxins, but instead produce insulin growth factor (IGF)-1, which supports neuronal survival in the recovery phase of acute neuronal injury (Schwartz et al. 2006; Colton 2009). A further neuroprotective phenotype in microglia, termed acquired deactivation, may be induced by IL-10 or by phagocytosis of apoptotic neurons, in contrast to necrotic cells which induce the aggressive M1 phenotype (Colton 2009).

Astrocytes provide neuronal support functions, yet they may also take part in immune responses, as they share many properties in common with microglia cells, including functional receptors for inflammatory stimuli and the capability to produce cytokines, ROS, and other immune mediators (Dong and Benveniste 2001; Farina et al. 2007). Similarly, microglia can function not only as immune cells, but also can provide neuronal support functions (Persson and Rönnbäck 2012).

Modulation of Microglia and Astrocytes by Glutamate Receptors

Activated microglia cells express mGluRs of almost all groups, and as described earlier, can release cellular products, which are toxic to neighboring neurons (Biber et al. 1999; Byrnes et al. 2009a). mGluR agonists modulate microglia-induced neurotoxicity: neurotoxicity is attenuated by signaling through mGluR1, mGluR5, mGluR3, and group III mGluRs, and promoted by signaling through mGluR2 (Taylor et al. 2003, 2005; Byrnes et al. 2009a). In an in vivo study, treatment with an mGluR5 agonist had a beneficial effect in a rat model of spinal cord injury, which included attenuation of microglial activation and neurotoxicity (Byrnes et al. 2009b). In an earlier study, injection of a group II agonist into the striatum of rats protected neurons from toxicity, and promoted the expression of brain-derived neurotrophic factor (BDNF) in microglia (Matarredona et al. 2001). In a more recent in vitro study, it was shown that glutamate can induce the production of BDNF and other neurotrophic factors from microglia, via activation of mGluR3 and NMDA receptor (Liang et al. 2010). It has also been reported that mGluR agonists can result in downregulation of proinflammatory agents in activated astrocytes (D'Antoni et al. 2008). These in vivo observations suggest that the healing process as a whole and microglial activation in particular, can be modified by mGluR signaling.

Adaptive Immunity: Interactions Between Effector and Regulatory T Cells

The development of a robust immune response is tightly controlled by populations of regulatory T cells, such as the naturally occurring T regulatory (Treg) cells and recently discovered natural killer T (NKT) cells. The naturally occurring regulatory T cells (Tregs), defined by the expression of $CD4^+CD25^+$ markers and the transcription factor forkhead box P3 (FoxP3), were shown to suppress immune response by other cells, and inhibit the proliferation of effector T cells (Shevach 2000; Hori et al. 2003; Josefowicz et al. 2012). Control of effector T cell expansion or activation by Tregs may involve cell-to-cell interactions, or act distally through secretion of regulatory cytokines (Sakaguchi et al. 2008). Moreover, naïve circulating T cells may also differentiate into Tregs upon encounter of their specific antigens without sufficient co-stimulation by relevant antigen-presenting cells (Sakaguchi et al. 2008). Interestingly, it was demonstrated that neurons may induce generation of Tregs, thus contributing to tight regulation of the immune response inside the CNS (Liu et al. 2006).

Increasing the number of T cells reactive to CNS-derived antigens by passive or active immunization was shown to be neuroprotective in various animal models of CNS injuries, including spinal cord-, optic nerve-, and closed head-injury (Moalem et al. 1999; Hauben et al. 2001; Kipnis et al. 2003). The spontaneous ability to manifest CNS-protective immune response was shown to be controlled by Tregs. It was demonstrated that recovery from CNS injury is impeded if the numbers of Tregs are increased, but improved if these cells are eliminated or decreased in number (Kipnis et al. 2004a, b). A major part in the influence of T cells and regulatory T cells on neuronal survival is mediated by their interactions with antigen-presenting cells, including infiltrating macrophages and monocytes, and resident microglia (Schwartz 2004; Kipnis et al. 2002, 2004a; Shechter et al. 2009; Schwartz and Shechter 2010; Beers et al. 2011). During CNS injury T cells can migrate into the damaged site, interact with activated microglia and produce neurotrophic factors and cytokines, which are capable of affecting the activity of resident microglia and astrocytes. To enable interactions between activated microglia and T cells, high expression of major histocompatibility complex Class II (MHC-II) and co-stimulatory molecules on microglia is needed, so that antigen-specific interactions will take place and feed-forward the neuroprotective processes (Butovsky et al. 2001). That in turn, restricts the spread of neuronal damage by limiting the release of neurotoxic factors and counteracting glutamate toxicity, thus helping the repair process (Schwartz et al. 2003; Schwartz 2004).

Despite the fact that Tregs were shown to interfere with the protective immune response in acute CNS injury models (Kipnis et al. 2002, 2004a), several findings in chronic models of CNS injury argued for their beneficial effect (Appel et al. 2010; Glass et al. 2010). Specifically, the protective involvement of Tregs was demonstrated in the early phase of ALS (Beers et al. 2011) and in a model of PD (Reynolds et al. 2010). In the case of ALS, neuroprotection was attributed to Tregs and/or T_H2 cells, while proinflammatory T_H1 or T_H17 lymphocytes were shown to be detrimental (Appel et al. 2010). Other studies have showed that the disease progression was exacerbated in T cell-deficient mice (Chiu et al. 2008), with both $CD4^+$ T cells and Tregs conferring neuroprotection (Banerjee et al. 2008). Importantly, in an animal model of stroke (Liesz et al. 2009), Tregs were found to be neuroprotective, with IL-10 signaling essential for their immunomodulatory effect. The difference between the effect of $CD4^+$ T cells and Tregs on neuronal survival in acute and chronic CNS injury stresses the importance of the timing and context of their involvement in the course of the disease. It is likely that while $CD4^+$ T cells are required for neuroprotection in the early stage of the injury, Tregs involvement is part of

the physiological cerebroprotective mechanism, occurring in later stage, aimed at termination of the post-injury immune response, a process that might be compromised under chronic neurodegenerative conditions (Finkelstein et al. 2012; Schwartz and Ziv 2008).

Natural Killer T (NKT) cells are another type of immunoregulatory lymphocytes, sharing markers with both Natural Killer (NK) and conventional T cells (Bendelac et al. 1995). These cells that can rapidly release large amounts of immunomodulating Th1 and Th2 cytokines, were suggested to act as negative regulators of autoimmunity (Hammond and Kronenberg 2003; van der Vliet et al. 2001). Recently, NKT cells were found to be elevated in an animal model of ALS, and their specific immunomodulation was neuroprotective resulting in recruitment of T cells into the affected spinal cord, and delay in the onset of the disease (Finkelstein et al. 2011). Interestingly, NKT cells were also shown to mediate immunosuppression following stroke via neuroadrenergic stimulation (Wong et al. 2011). It remains an open question whether NKT cells play a role in other neurodegenerative conditions in the CNS, including organophosphate toxicity.

The Immunomodulatory Effects of Glutamate in Adaptive Immunity

The possible role of glutamate in mediating neuronal protection by T lymphocytes has been implied in earlier studies (Schori et al. 2002). The experimental evidence suggests that glutamate modulates T cell neuroprotection via mGluRs. Studies undertaken in order to better understand the roles of different receptors in glutamate toxicity have shown that glutamate-induced toxicity, even when mediated by the NMDA receptor, differs from NMDA-induced toxicity in the following findings (Schori et al. 2002): (i) NMDA-induced toxicity can be completely blocked by the use of its receptor antagonist, but glutamate-induced toxicity is only partially inhibited by NMDA antagonists, and not in all cases. The opposite is also true. Compounds that protect neurons against glutamate-induced toxicity, do not protect them from NMDA-induced toxicity (ii) NMDA-induced toxicity occurs within 24 h, unlike the death process induced by glutamate, which is more prolonged. More importantly, (iii), T cells protect retinal ganglion cells from glutamate but not from NMDA-induced toxicity (Schori et al. 2002). These findings indicated that glutamate stimulates a self-protective pathway alongside the destructive pathway, and the final outcome is determined by the balance between the two. Subsequently, a mechanism for the role of T cells in glutamate toxicity has been proposed and demonstrated (Schwartz et al. 2003; Shaked et al. 2005). According to this mechanism, T cells that migrate to a lesion site secrete interferon (IFN)-γ which induces in activated microglia enhanced expression of MHC-II, co-stimulatory molecules, and the glutamate transporter EAAT2, as well as the transporter EAAT1 on astrocytes. Thus, glutamate uptake and glutamate homeostasis that were disrupted by the oxidative inflammatory environment are restored. Concomitantly, the antigen-specific interactions of microglia with T cells further enhance the production of IFN-γ, thus regulating the neuroimmune response.

T lymphocytes express functional iGluRs and mGluRs, which modulate regulatory cascades and affect activity-related functions (Pacheco et al. 2007). Of group I mGluRs, mGluR5 is expressed constitutively while mGluR1 expression is induced upon T cell activation. Signaling via mGluR5 was found to inhibit activation of resting T lymphocytes while signaling via mGluR1 reverses this repression and allows proliferation and cytokine secretion (Pacheco et al. 2007). Along this line, Pacheco et al. (2007) proposed that mGluR1-expressing, autoantigen-specific, $CD4^+$ T lymphocytes which infiltrate the CNS, are stimulated by glutamate to secrete IFN-γ which induces EAAT2 expression and glutamate uptake by microglia, so they can replace lost or impaired astrocytes, as shown by Shaked et al. (2005).

A novel mechanism of neuroinflammation control by glutamate via mGluR signaling was demonstrated recently, involving dendritic cells (DCs) (Fallarino et al. 2010; Hansen and Caspi 2010). In this study, the effect of mGluR4 on the course of experimental autoimmune encephalomyelitis (EAE), an animal model of MS, was studied in the mGluR4 gene knockout mice. The disease course in the knockout mice was exacerbated, and the immune status in the deficient mice revealed a high prevalence of T_H17 $CD4^+$ cells, compared to wild-type mice, which showed a higher prevalence of Treg cells. These studies led to the understanding that mGlur4 signaling skews the differentiation of T lymphocytes from proinflammatory T_H17 to Treg cells, by modulating the cytokine response in stimulated DCs, thus reducing the inflammation and neurodegeneration in wild-type, but not in mGluR4 knockout EAE animals. These results demonstrated a new role for glutamate as an immunomodulator that affects the adaptive immune response (Fallarino et al. 2010; Hansen and Caspi 2010).

CNS-specific T lymphocytes mediate protective immunity as providers of cytokines that modulate microglial activation. The immediate "first responder" may be T_H1 lymphocytes that provide IFN-γ for neuroprotective microglial modulation (Schwartz et al. 2003; Shaked et al. 2005). Glutamate, via mGluR1 signaling, may enhance the production of IFN-γ by infiltrating T cells that interact with antigen-presenting microglia (Pacheco et al. 2007). The role of these T cells in neuroprotection from OP or glutamate toxicity was demonstrated in retinal ganglion cells

(Schori et al. 2005), and in their early recruitment in OP-poisoned rats by poly-YE (Finkelstein et al. 2012).

The Concept of Immunomodulatory Treatment in OP Poisoning

Adaptive Immunity: Teff and Treg Lymphocytes in OP Poisoning

The requirement of adaptive immunity for neuroprotection in OP-invoked glutamate-mediated degeneration was first demonstrated in a retinal ganglion model (Schori et al. 2005). In that study, the protective role of T cells was shown by increased neurodegeneration in T cell-deficient mice. As described in the previous sections, it was demonstrated that neuroprotective immune response can be achieved by direct T cell activation or by transient removal of the suppressive effect of Tregs (Kipnis et al. 2002; Schwartz and Kipnis 2005). Poly-YE, a high-molecular-weight (22–45 kD) copolymer that is known to exert modulatory effects on the immune system (Vidovic and Matzinger 1988; Cady et al. 2000), was shown to be capable of down-regulating the activity of regulatory T cells, and was found to be neuroprotective in animal model of stroke (Ziv et al. 2007). On the basis of the striking similar pathology seen in seizure-related brain damage and in other CNS insults, in which glutamate has a central role, mainly stroke (Ballough et al. 2008), we have decided to see whether similar immune interventions can modify the course of OP intoxication. In the recent study of Finkelstein et al. (2012), protection by poly-YE was studied in rats exposed to the nerve agent soman and the organophosphate pesticide paraoxon. Treatment with poly-YE reduced neuroinflammation and cognitive impairment, and enhanced recovery. The characteristic immunological finding was an early (7 days post-intoxication with paraoxon) recruitment of $CD4^+$ T cells into the CNS in the poly-YE-treated animals, while in non-immunized intoxicated controls this increase was detected only at the late post-exposure time point (28 days), when CNS T cell levels in the immunized animals returned to normal levels. Importantly, CNS-infiltrating T cells contained a proportion of Treg cells ($CD4^+CD25^+Foxp3$), indicating a central role for regulation of neuroinflammation by the T helper–Treg immune axis.

Thus, although the success of poly-YE in enhancing recovery in the models of CNS injury was attributed to a transitory suppression of Tregs (Ziv et al. 2007) that interfere with the protective action of T cells, the subsequent infiltration of Tregs could provide the anti-inflammatory environment required for termination of the initial protective immune response in the recovery processes (Liesz et al. 2009; Finkelstein et al. 2012). The time course of T cell recruitment in the study of Finkelstein et al. (2012) suggested that the contribution of poly-YE was the acceleration of a physiological protective response. Consequently, the results of Fallarino et al. (2010), indicating a role for mGlur4 signaling in skewing T cell differentiation toward Tregs, are consistent with an active role of Tregs in protection and recovery from glutamate toxicity in the later phase of OP intoxication.

Glutamate and Neuroimmune Interactions in OP Poisoning

The studies of Schori et al. (2005) and Finkelstein et al. (2012) outlined above gave a strong support to the concept of involvement of the immune system in the processes taking place in the OP-poisoned CNS and the poisoning outcome. Overall, the neuroimmunological model of OP-induced CNS poisoning is shown in Fig. 1, consisting of the cholinergic–glutamatergic crisis, neuroinflammation, and finally tissue regeneration, repair and recovery, which may be either complete or partial. The immunomodulatory effects of glutamate, either detrimental or beneficial, centered mainly at the neuroinflammatory phase, are depicted schematically in Fig. 2. They are arranged in three tires: (i) innate immunity, involving microglia and astrocytes, whose activation states are pivotal in affecting neuronal survival; (ii) adaptive immunity, exerted by Teff lymphocytes; and (iii) suppression of inflammation by Tregs, whose differentiation is directed by glutamate-modulated DCs.

Clinical and Research Implications

The pathogenesis of CNS OP/NA poisoning is a typical acute neural insult. Although much of the non-OP research cited in this article was oriented toward chronic neurodegenerative diseases, many insights and implications are relevant in the acute and sub-acute OP context. The chronic diseases are described in recent literature as a recurrent loop of inflammation and neurodegeneration which kindle each other and go out of control (Glass et al. 2010), while the aim of the intervention is to break this vicious circle. In the acute injury, the goals are to minimize neuronal loss, control neuroinflammation, and assist tissue regeneration, and thus prevent long-term effects. One important insight is that the innate immune processes that take place are basically beneficial, designed to remove remains of dead cells and prepare for neuroregeneration, while the destructive events are epiphenomena that occur when normal control is overwhelmed or impaired. The immune response in the CNS, classically conceived as detrimental, is currently regarded as supportive under physiological conditions, and

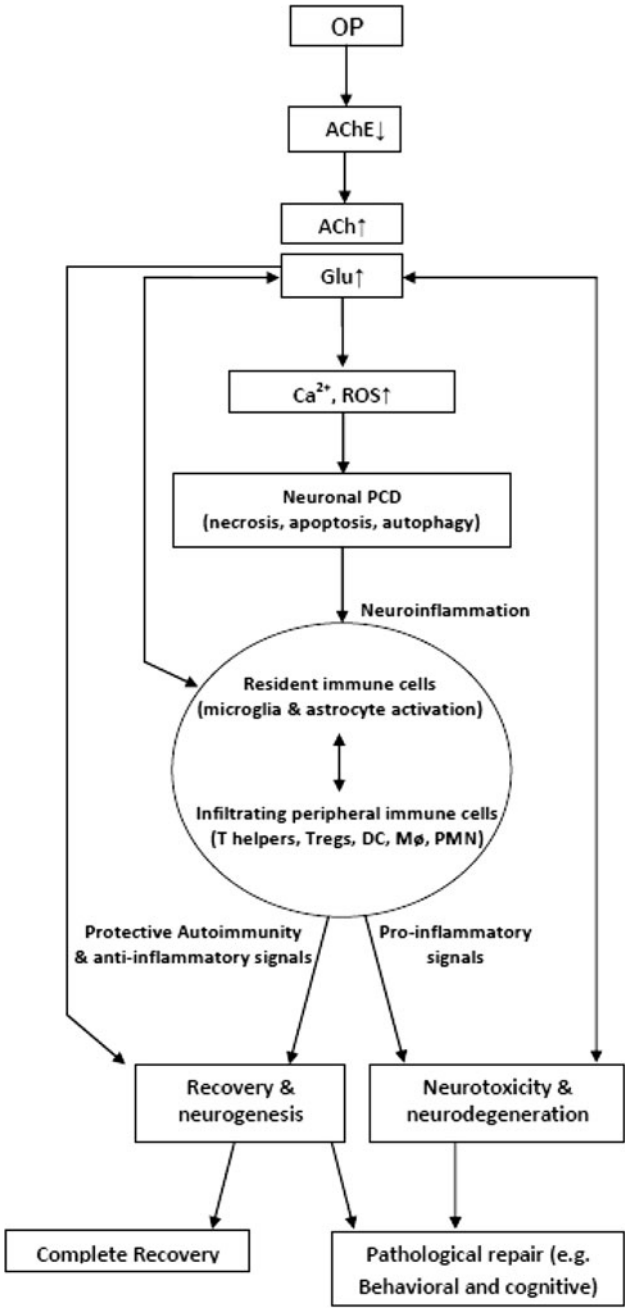

Fig. 1 Suggested neuroimmunological model of OP-induced CNS poisoning

having beneficial effects when boosted in disease (Schwartz et al. 2003; Schwartz and Ziv 2008).

The same is true when focusing on glutamate, which was shown as both a major neurotoxin and a beneficial mediator. The close functional relationship of glutamate and immune processes are demonstrated in the protective actions of the immune system against glutamate toxicity, and the reciprocal action of glutamate as an immunomodulator capable of enhancing the protective immune response (Schwartz et al. 2003; Pacheco et al. 2007; Hansen and Caspi 2010). Therefore, any intervention should avoid compromising the essential functions of glutamate, which was not the case when classical NMDAR antagonists were tested in clinical trials (Papadia and Hardingham 2007). A well-studied approach is to target the metabotropic glutamate receptors, in which some beneficial effects were demonstrated in animal models of CNS injury (Bruno et al. 2001; Byrnes et al. 2009a, b). Another approach was to reduce glutamate load in the CNS following OP poisoning. This was achieved by enhancing brain glutamate clearance through activating blood glutamate scavenging system (Eisenkraft et al. 2008). The efficacy of the immune response in the control of glutamate toxicity was demonstrated in several neurodegenerative models, including a model where neuronal degeneration was induced by direct exposure to glutamate but not NMDA (Schori et al. 2001, 2002). Based on these considerations, the appropriate strategy toward glutamate in the management of CNS injuries, OP intoxication included, is not to block it but rather to enhance its beneficial effects, either by pharmacological means or by boosting the spontaneous immune response.

Those surviving the acute phase of OP poisoning may suffer from long-term effects, which result especially from CNS injury. The long-term effects include neurological, cognitive, or behavioral deficiencies which vary from mild and detectable only by very sensitive neurological or psycho-cognitive tests, to severe and debilitating (Hoffman et al. 2007; Sidell et al. 2008). Follow-up studies in surviving victims and exposed first responders from the 1994 to 1995 sarin terror attacks in Japan, revealed the occurrence of neurological, cognitive, or behavioral deficiencies of varying degrees (Okomura et al. 2005; Yanagisawa et al. 2006; Hoffman et al. 2007), as well as structural changes in the brain, detected and quantified by brain imagery analysis (Yamasue et al. 2007). Another case of long-term effects attributed to cholinesterase inhibitors exposure concerns the US 1991 Gulf War veterans (Golomb 2008). These veterans included cohorts allegedly exposed to low levels of the NAs sarin and cyclosarin, released unknowingly during the demolition of a large Iraqi ammunition depot (McCauley et al. 2001). In these cohorts, minor cognitive deficiencies and structural changes in brain imagery were found (Proctor et al. 2006; Heaton et al. 2007; Chao et al. 2010). Even though the evidence linking these clinical findings to NA exposure is limited (Brown 2006), there is little reason to doubt that exposure to cholinesterase inhibitors has left its footprints, as seen in the minor white matter or gray mater degeneration observed in these studies (Chao et al. 2010).

Cognitive and emotional deficiencies were observed in behavioral studies in rodent models exposed to NAs (Weissman and Raveh 2008; Grauer et al. 2008; Collombet 2011). In the case of seizure-inducing exposure, some of the

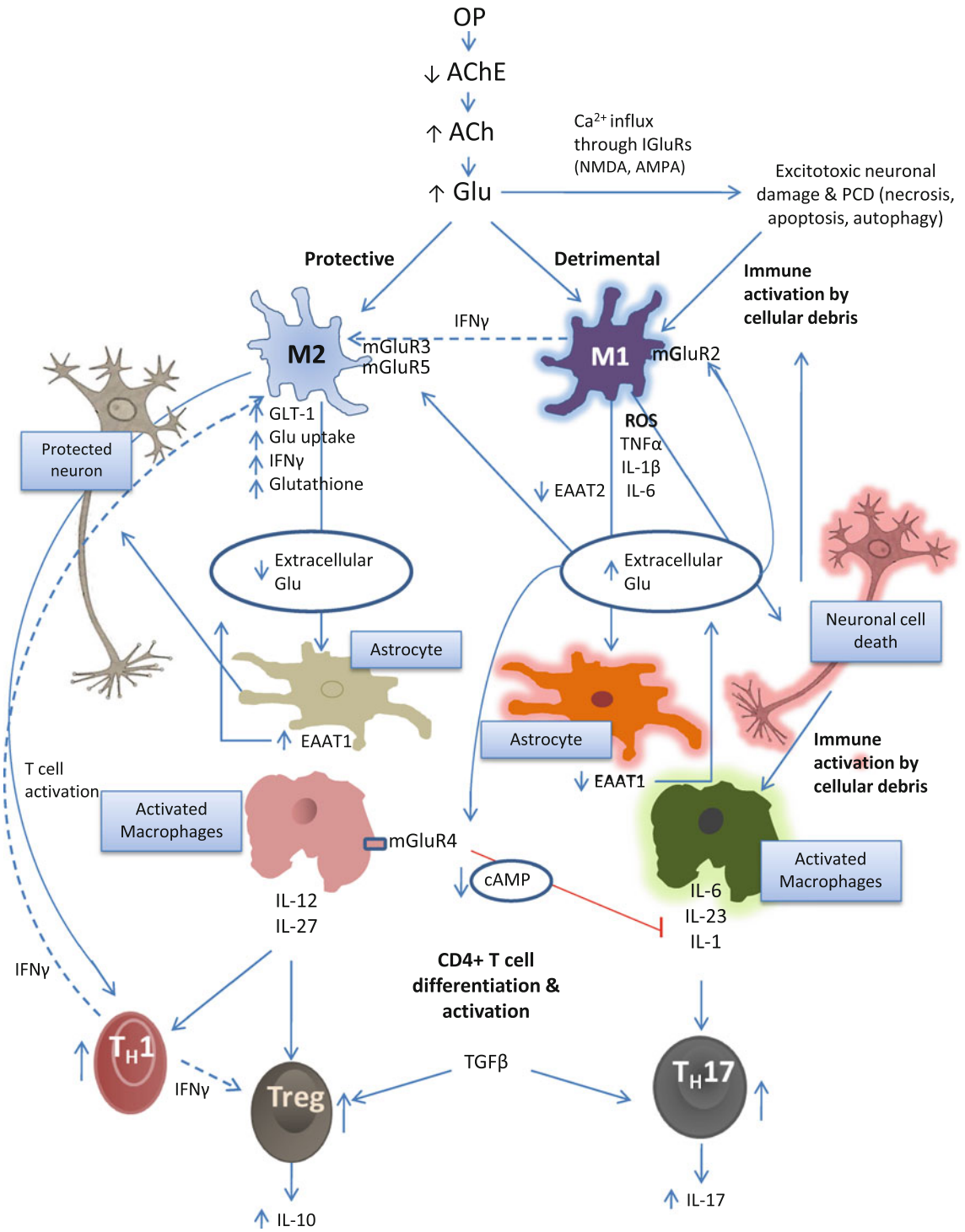

Fig. 2 Schematic description of the immunomodulatory effects of glutamate, including detrimental and beneficial effects, mainly at the neuroinflammatory phase. These effects involve three leading systems: innate immunity, involving microglia and astrocytes, whose activation states are pivotal in affecting neuronal survival; adaptive immunity, exerted by Teff lymphocytes; and suppression of inflammation by Tregs, whose differentiation is directed by glutamate-modulated DCs

mental deficiency effects can be attributed directly to neuroinflammation, as in other models (Yirmiya and Goshen 2011). The delayed mental effects in acute, or low level chronic exposure to organophosphates, may be generated in related, although different, mechanisms. One possible mechanism is chronic neuroinflammation, limited in spatial spread and intensity. Support for this mechanism comes from studies showing sustained microglial activation, concomitant

with spatial learning deficiency, after exposure of rats to sarin (Grauer et al. 2008), and astroglial scarring in the brains of soman-exposed rats (Collombet 2011), or other models like a late wave of chronic inflammation in rats recovering from spinal cord injury (Byrnes et al. 2011). Another possible mechanism may be aberrant integration of new neurons in neural circuits during the regeneration observed at the late stages of OP intoxication (Collombet 2011), similarly to other models of epileptogenesis (Parent and Murphy 2008). It follows that management practices, including immune-based approach, targeted at glutamate toxicity at the right time after exposure to NAs may diminish neuronal damage and the resulting pathological recovery and mental impairment, ease the rehabilitation of the severely injured and prevent the non-life-threatening, but significant, after effects of low level exposure. Importantly, animal studies have shown genetic variation in the ability to be protected from neuronal damage through immune-related mechanisms (Kipnis et al. 2001). As human populations are heterogeneous, it is more than logical to expect that not every patient will be amenable to a given intervention, so it is desirable to explore a range of interventions, with the visionary possibility of predicting the optimal intervention for the individual patient.

Conclusions

In summary, the issues discussed highlight a combination of two current issues in neurobiology, the role of glutamate and interactions of the CNS and the immune system. Both matters, arising in the context of acute and chronic CNS injuries, were shown as a double-edged sword, detrimental or beneficial. Both issues were shown to converge not only in the extensively studied areas of neurodegenerative diseases, CNS trauma, stroke, and epilepsy, but also to the more specific area of OP toxicity. The empirical study on immunological protection from organophosphate-induced toxicity, which is in its infancy, has shown to be promising in borrowing insights, concepts and novel medical treatment strategies from the growing fields of neurodegeneration and neurotrauma research, which has undergone more than a single paradigm shift concerning the CNS-immune system relations and their roles in neural damage and repair. These have contributed to our understanding and ability to manage an aspect that has been more unknown than neglected—the long-term effects of NA poisoning.

Conflict of interest The authors declare no conflict of interests.

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