HHS Public Access

Author manuscript

Neurochem Res. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Neurochem Res. 2016 February ; 41(0): 144–155. doi:10.1007/s11064-015-1746-3.

Cerebral Response to Peripheral Challenge with a Viral Mimetic

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Abstract

It has been well established that peripheral inflammation resulting from microbial infections profoundly alters brain function. This review focuses on experimental systems that model cerebral effects of peripheral viral challenge. The most common models employ the induction of the acute phase response (APR) via intraperitoneal injection of a viral mimetic, polyinosinic-polycytidylic acid (PIC). The ensuing transient surge of blood-borne inflammatory mediators induces a “mirror” inflammatory response in the brain characterized by the upregulated expression of a plethora of genes encoding cytokines, chemokines and other inflammatory/stress proteins. These inflammatory mediators modify the activity of neuronal networks leading to a constellation of behavioral traits collectively categorized as the sickness behavior. Sickness behavior is an important protective response of the host that has evolved to enhance survival and limit the spread of infections within a population. However, a growing body of clinical data indicates that the activation of inflammatory pathways in the brain may constitute a serious comorbidity factor for neuropathological conditions. Such comorbidity has been demonstrated using the PIC paradigm in experimental models of Alzheimer's disease, prion disease and seizures. Also, prenatal or perinatal PIC challenge has been shown to disrupt normal cerebral development of the offspring resulting in phenotypes consistent with neuropsychiatric disorders, such as schizophrenia and autism. Remarkably, recent studies indicate that mild peripheral PIC challenge may be neuroprotective in stroke. Altogether, the PIC challenge paradigm represents a unique heuristic model to elucidate the immune-to-brain communication pathways and to explore preventive strategies for neuropathological disorders.

Keywords

inflammation; sickness behavior; neuropathologies; viral infections; comorbidity; neuroprotection

1. Introduction

The existence of active communication pathways between the immune system and the brain has been well established. A stellar example is the assemblage of behavioral symptoms, such as, fever, cognitive dysfunction, anxiety, depression, anhedonia, malaise, anorexia, adipsia, lethargy and fatigue elicited by peripheral infections and collectively referred to as “sickness behavior” (1-3). Sickness behavior is thought to promote optimal recovery and survival by altering the priorities of the affected individuals to conserve resources and to forfend the

spread of infection within the population. Mechanisms of this immune-to-brain communication involve relaying inflammatory signals from the site of infection to the brain whereby they activate cerebral innate immunity via several humoral and neural pathways (1, 3). Thus, the blood-borne inflammatory mediators can be directly transported through the blood-brain barrier (BBB) or through circumventricular organs (CVO) to the brain parenchyma. Alternatively, the circulating mediators may be transduced by activating the BBB and/or CVO cells resulting in a secretion of secondary mediators into the cerebral parenchyma. Within the cerebral parenchyma, the peripherally-generated and/or BBB/CVO-generated mediators activate cerebral innate immune cells, chiefly astrocytes and microglia that generate tertiary mediators. Tertiary mediators can also be generated by neurons that express receptors cognate to a slew of inflammatory mediators. Consequently, the brain is exposed to the peripherally-generated inflammatory agents, the cerebrally-generated agents or a combination thereof. The interplay of these agents creates an intricate, yet poorly understood, network of autocrine/paracrine and intracellular signaling pathways that interact with neurotransmitter, neuropeptide and neuroendocrine systems. This neuroinflammatory response alters brain function leading to the behavioral symptoms of sickness. In addition, vagal as well as other afferent pathways may detect inflammatory signals in the periphery and relay them directly to specific brain regions that orchestrate sickness behavior.

This review focuses on cerebral response to peripheral viral challenge. The main thrust is on the characterization of the most frequently used experimental model in which the acute phase response (APR) is instigated by a viral mimetic, polyinosinic-polycytidylic acid (PIC). Moreover, the applicability of this paradigm to study several neuropathological conditions as well as the most representative findings is presented.

2. Viral model

2.1. dsRNA

Studies addressing the mechanism by which the immune system affects brain function have largely employed the stimulation of the peripheral innate immunity with pathogen-associated molecular patterns (PAMPs) to mimic microbial infections. The most widely employed experimental paradigms induce APR to bacterial infection via systemic challenge with lipopolysaccharide (LPS), a ubiquitous component of the cell wall of gram negative bacteria. Relatively fewer studies address the effects of anti-viral APR on the brain. This experimental paradigm involves immune challenge with double stranded RNA (dsRNA). dsRNA is a signature PAMP of viral infection, because the vast majority of viruses either contain dsRNA in their genomes or generate dsRNA species during their lifecycle (4, 5). For example, viruses with dsRNA genomes may expose this PAMP in defectively packaged virions. Substantial amounts of dsRNA intermediates are generated during the replication of positive-strand ssRNA viruses, while DNA viruses generate dsRNA intermediates during overlapping convergent transcription. However, no detectable quantities of dsRNA are generated by negative-strand ssRNA viruses (5). Mammalian cells express several receptors that detect the presence of extra- and intracellular dsRNA in a sequence-independent fashion, e.g., Toll-like receptor 3 (TLR3), retinoic acid-inducible gene 1 (RIG-1), melanoma differentiation-associated protein 5 (MDA-5) and protein kinase R (PKR)(6). dsRNA

released from infected cells is recognized by these receptors on neighboring cells and rapidly triggers an antiviral response characterized by the expression of type I interferons (IFNα and IFNβ), as well as a plethora of other cytokines and inflammatory mediators. This early event in viral infection represents the first line of anti-viral defense critical for containing the spread of viral infections long before the adaptive immunity against viral antigens becomes effective.

2.2. PIC

A synthetic dsRNA, PIC, has been widely used as a potent inducer of antiviral APR (7-9). Systemic administration of PIC has been shown to induce symptoms of sickness behavior in laboratory rodents (9-16) that is congruent with behavioral effects of peripheral viral infections in humans (17-19). These studies have also demonstrated that PIC challenge models APR to generic viral infections, and that this APR is the major inducer of cerebral response. Although models using bona fide viral infection represent more clinically relevant approach, the PIC-based model offers several heuristic advantages for mechanistic analysis of immune-to-brain communication. For example, in contrast to viral inoculation that entails a prolonged and nonsynchronous incubation time before eliciting innate immune response, the inflammatory response to dsRNA is very rapid, allowing hour-by-hour kinetic analyses. There are no comorbid effects of pathogen-associated tissue damage as the biological activity of PIC is restricted to the stimulation of the innate immune response. Furthermore, the possibility for confounding involvement of adaptive immunity such as antibodies and T cells resultant from prior exposure of animals to viral or cross-reactive proteins is eliminated. Finally, PIC is noninfectious, and thus, the experiments can be conveniently performed under standard laboratory conditions. Consequently, peripheral PIC challenge provides a unique model of peripheral viral infection that allows analysis of humoral communication along the immuno-neural axis. The inflammatory pathways instigated by PIC challenge are depicted in Fig. 1.

2.3. PIC vs. LPS

Although both the LPS and PIC paradigms of intraperitoneal immune stimulation provide valuable experimental models, they differ in several aspects. LPS activates Toll-like receptor (TLR) 4 while PIC acts primarily through TLR3. These two receptors employ different signaling pathways that generate inflammatory mediators germane to antibacterial and antiviral APR, respectively. These diverse APR profiles may in turn elicit dissimilar inflammatory responses in the brain. Also, the pharmacokinetics of LPS and PIC are quite dissimilar. LPS is a stable amphipathic molecule that rapidly passes from the peritoneal cavity into the bloodstream (20, 21), and thus, can activate innate immune cells throughout the body including the BBB and CVO cells. Thus, in the LPS paradigm the brain is challenged by a combination of LPS and LPS-induced peripheral inflammatory mediators. In contrast, PIC is a large, charged molecule that is rapidly degraded by ubiquitous RNases in the body fluids (22). Intraperitoneally injected PIC does not reach the circulation and its cerebral effects are mediated by blood-borne inflammatory factors (23).

In line with the above disparities in pharmacokinetics and pharmacodynamics between LPS and PIC, notable differences in behavioral effects of these two inflammagens have been

reported. For example, Hopwood and collaborators found PIC to be less potent in inducing anorexia and lethargy that LPS in rats (24). They also observed PIC to be a less effective pyrogen than LPS.

Recently, cerebral response to LPS and PIC has been analyzed at the transcriptome level. At 48 h after LPS challenge, 71 genes were found dysregulated (25), while 260 genes were dysregulated by PIC (26). Only 23 genes were commonly affected by both inflammagens, whereas 48 and 237 genes were dysregulated exclusively by LPS and PIC, respectively. This comparison further substantiates the dissimilarity in neuroinflammatory response of the brain instigated by LPS vs. PIC.

3. Cerebral response

3.1. Behavior

Cunningham and colleagues have provided the first comprehensive assessment of cerebral response of mice to PIC challenge at the behavioral and molecular levels (27). Their findings show the burrowing activity to be the most severely reduced by intraperitoneal injection of PIC. This transient reduction reaches a nadir at 6 h and returns to control level by 48 h after PIC challenge. The animals also display a transient decrease in locomotor activity. These behavioral changes are accompanied by a mild hyperthermia and a loss of body weight. All these effects are dependent on PIC dose in a range of 2 to 12 mg/kg body weight. Moreover, successive challenge at one or three weeks does not induce behavioral tolerance to PIC. Also, no inflammatory tolerance has been shown in mice receiving multiple (seven) daily injections of PIC (28). An earlier study in rabbits, found systemic administration of PIC to increase body temperature and to activate the hypothalamo-pituitary-adrenocortical axis (29).

The burrowing test that provides a sensitive assessment of behavioral dysfunction in rodents (30), is the most discriminatory assessment of PIC-induced sickness behavior as the burrowing activity is reduced by approximately 95% at 6 h (27, 31). We have recently shown that the rearing activity of mice challenged with PIC is equally reduced at 6 h (26). In contrast to the burrowing test that is rather intricate and time-consuming (2 h testing time), the rearing test is a simple procedure that can be completed within 15 min. Consequently, the rearing test provides a convenient and sensitive procedure for gauging sickness behavior.

3.2. Molecular level

PIC challenge triggers a robust surge of peripheral cytokines in mice. This is manifested as a transient elevation of blood levels of interferon β (IFNβ), interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and IL1β (26, 27). Blood levels of these cytokines peak at 3 h post-injection, rapidly decline by 6 h and gradually dwindle to the basal level. The cytokine surge is concomitant with transient upregulation of genes encoding IL-1β, IL-6, TNFα and IFNβ in the hippocampus and hypothalamus (27). We have extended this study and showed that the cerebral response is global rather than regional as it is featured in all major parts of the brain, i.e., the cerebellum, forebrain and brainstem (23, 31, 32). In all brain regions, the expression of a multitude of inflammatory and stress genes is robustly upregulated from several- to several thousand-fold. Also, injection of blood plasma from PIC-challenged into

naïve mice mimics the effect of PIC by instigating the upregulation of cerebral genes (23). Because PIC does not reach the circulation (23), these results indicate that the cerebral neuroinflammatory response is mediated by peripherally-generated, blood-borne inflammatory factors. The kinetics of blood-borne cytokines and cerebral gene expression is presented in Fig. 2.

Our recent whole genome transcriptome analysis revealed a robust polygenic response in the hippocampus of PIC-challenged mice (33). Thus, 625 genes were found to undergo dynamic dysregulation between 0 and 48 h after the challenge. As expected, the majority of these differentially expressed genes were related to immune and inflammatory processes of both the innate and acquired immunity. However, a plethora of genes related to neurotransmission were also dysregulated. Moreover, ten microRNAs that modulate both neural and immune functions or are associated with seizure pathology also featured differential expression following PIC challenge (26). Altogether, these results indicate an extensive genomic reprogramming in the hippocampal cells instigated by peripheral antiviral response.

4. Mechanistic considerations

The major inflammatory mediators generated either in the periphery or in the brain in response to PIC challenge are potent effectors of neurotransmission. These effects are likely to be mediated or at least contribute, to the development of behavioral alterations as exemplified below.

4.1. Cytokines

IL-1β is the primary cytokine responsible for the induction of fever following PIC injection (10). Intraventricular injection of IL-1β also induces anorexia (34). IL-1β inhibits voltage-dependent calcium channel currents in cultured hippocampal and cortical neurons (35, 36), resulting in the reduction of presynaptic glutamate release (37) and impaired long term potentiation (LTP) (38, 39). At low concentrations, IL-1β potentiates NMDA response in the hippocampal neurons (40, 41), whereas the opposite effects is elicited at high concentrations (42). In a similar concentration-dependent fashion, IL-1β may enhance (43) or reduce (44) the GABAergic activity in hippocampal neurons. Neuronal excitability may be additionally impacted by IL-1β-engendered impairment of glutamate uptake (45) by astrocytes. IL-6 also has a biphasic modality effect on neuronal excitability (46-48). IL-6 inhibits LTP (49) and impairs cognitive functions (50). Moreover, systemic injection of IL-6 decreases interstitial dopamine level in the nucleus accumbens (51). TNFα increases surface expression of AMP A receptors (52, 53), leading to the enhancement of excitatory synaptic efficacy. TNFα also promotes endocytosis of $GABA_A$ receptors, and thus, decreases the strength of inhibitory synapses (53). This cytokine also reduces the outward potassium current in cortical neurons (54), facilitates synaptic scaling (55), and inhibits LTP (38). In astrocytes, TNFα increases glutamate release (56) and reduces the capacity to buffer extracellular potassium (57). IFNβ was recently shown to mediate several traits of sickness behavior, i.e., hypothermia, anhedonia and anorexia (58). This antiviral cytokine enhances the excitability of neocortical neurons in culture (59), CA3 pyramidal neurons in hippocampal slice cultures (60) and CA1 pyramidal neurons in acute hippocampal slices (61). However, in striatal medium spiny

neurons, IFNβ attenuates glutamatergic neurotransmission (62), raising the intriguing possibility that IFNβ action depends on the type of targeted neurons. IFNβ also reduces expression of the glutamate/aspartate transporter (GLAST) in astrocytes (61).

4.2. Chemokines

Nearly half of the genes encoding mouse chemokines are upregulated by PIC challenge (23). Of a particular interest are the genes encoding eight chemokines, i.e., CXCL1, CXCL2, CXCL9, CXCL10, CCL2, CCL4, CCL5 and CCL7 genes. These genes feature upregulation from 60 to 4000 fold over the baseline. PIC challenge also upregulates three genes encoding receptors that bind most of these chemokines, i.e., the *Cxcr2, Ccr1* and *Ccr5* genes. Signaling pathways triggered by the cognate chemokines are potent modulators of neuronal activity and behavior. For example, CXCL9/10 are ligands of the CXCR3 receptor, whose activation inhibits long-term potentiation, elevates intracellular calcium and increases electrical activity of hippocampal neurons (63, 64). CXCR3 ligation also alters the expression of several glutamatergic and GABAergic receptors (65). CXCL1 and CXCL2, the agonists of CXCR2, enhance glutamatergic receptor activity and modulate electrical activity of Purkinje neurons (66-68). The activation of CXCR2 also reduces calcium currents and the excitability of septal neurons (69). The ligation of CCR2, the receptor of CCL2 and CCL7, inhibits GABAergic responses of spinal neurons (70), increases dopaminergic neuron discharge and dopamine release in the substantia nigra (71). The ligation of CCR1 that binds CCL4 was reported to increase NMDA-evoked Ca2+ signals and NMDA receptor levels in the hippocampal neurons (72). Behaviorally, the ligation of CCR1 and CCR5 evokes a febrile response (73-75). Ligands of CXCR3, CCR1, CCR2 and CCR5 suppress food intake (35, 76, 77), while the ligation of CCR2 increases locomotor activity (71). Neuronal as well as glial expression of the chemokines and their cognate receptors (78, 79) implicates the existence of intricate paracrine/autocrine pathways that affect neuronal activity. Consequently, complex intercellular chemokine signaling networks in the brain are likely to underscore the development of sickness behavior induced by peripheral inflammatory signals generated in response to PIC challenge.

4.3. COX2

The inducible cyclooxygenase (COX2) is the central enzyme in the biosynthesis of important inflammatory mediators, viz. prostaglandins and prostacyclin. COX2 upregulation has been demonstrated in endothelial cells in the mouse brain following systemic PIC challenge at both the message and protein levels (27). This is congruent with similar studies in the guinea pig brain (80). Moreover, the inhibition of COX2 has been shown to obliterate febrile response induced by PIC challenge in rabbits (29) and in guinea pigs (80). Together, these results support the role of endothelial COX2 as a transducer of blood-borne inflammatory signals to the brain parenchyma. In addition, prostaglandins have detrimental effects on cognitive functions by the impairment of learning and memory processes (81, 81). In vitro, the PGE2 prostaglandin increases excitability and synaptic transmission of hippocampal neurons (82) and enhances astrocytic glutamate release (56).

4.4. NO and CX3CL1

The upregulation of nitric oxide (NO) synthase type 2 (NOS2) is considered to be the integral element of neuroinflammation. However, in spite of a robust up-regulation of chemokines and cytokines, we observed no up-regulation of the *Nos2* gene expression in the brains of mice challenged with PIC (32). Also, we did not observe upregulation of the gene encoding the CX3CL1 chemokine, aka, fractalkine (23). Both NO and CX3CL1 can mediate brain tissue damage. NO is a highly reactive free radical that has diverse harmful effects on neuronal function, causing neuronal cell injury and death (83). CX3CL1 is a potent proinflammatory chemokine that promotes the proliferation of microglia and facilitates their activation into the pro-inflammatory and cytotoxic M1 phenotype (84). Consequently, PIC challenge models a “physiological” cerebral response expected during peripherally restricted infections that elicits protective sickness behavior in the absence (or suppression) of detrimental neuroinflammatory bystander effects.

5. Neuropathological models

Although sickness behavior per se represents a physiological adaptation that facilitates the healing process, in neurodegenerative disorders and in aged brains, the transient stimulation of cerebral immunity may enhance preexisting inflammatory levels, and consequently, promote further tissue destruction. In this context, even an innocuous virus may exacerbate neuropathological events. Such infectious triggers may underlie neuropathological deteriorations that are otherwise classified as idiopathic. In fact, peripheral viral infections are emerging as comorbid factors in neurodegeneration. For example, peripheral infections exacerbate cognitive dysfunction in Alzheimer's disease (AD) (85-89) and age-related dementia (90). The effects of peripheral viral infection on neuropathological conditions using the PIC model have been addressed in several preclinical studies as presented below.

5.1. Alzheimer's disease

The induction of cognitive impairments has been reported in animals peripherally challenged with PIC. For instance, PIC challenge disruptes hippocampus-dependent memory consolidation as seen from a worsening of performance on the contextual fear conditioning (CFC) test in mice (91). In addition, the cerebral response to PIC challenge has been shown to be exacerbated in the aging as compared to young brain (92). Together, these results indicate a possible link between a viral challenge and AD. Indeed, a subsequent study (28) revealed that the administration of seven daily i.p. injections of PIC elicited over a two-fold increase in the levels of the amyloid-beta peptide ($A\beta_{1–42}$), a pathological signature of AD, in the hippocampus. Aβ production was concomitant with a profound cognitive dysfunction assessed by the CFC test. A linear regression analysis revealed that the increase in hippocampal Aβ greatly contributed to the deficient memory consolidation following PIC challenge. These data buttress the contention that viral infections exacerbate cognitive deficits in AD.

5.2. Prion disease

Field and collaborators reported that PIC challenge exacerbated neurodegeneration in the ME7 prion-diseased mice (93). A single intraperitoneal injection of PIC impaired motor co-

ordination and muscle strength in ME7 but not in control mice. Three consecutive injections of PIC to ME7 mice at 2 week-intervals dramatically accelerated the neurological decline in a cumulative manner. At the molecular level, PIC challenge upregulated the expression of IFNα, IFNβ and two proinflammatory cytokines, i.e., IL-1β and IL-6, in the hippocampus and hypothalamus of diseased mice. Also, several IFN-responsive genes featured significant upregulation, indicating cerebral generation of type I IFNs. Histological examination revealed microglial activation with increased number of IL-1β positive microglia in the periventricular and dentate gyrus regions. There was also an increased COX2 staining of the endothelial cells. Moreover, PIC challenge activated proapoptotic pathways as seen from upregulated levels of mRNA encoding the dsRNA-dependent protein kinase (PKR) and Fas, as well as from an increase in TUNEL positive cells. Altogether, these results indicate the role of type I IFN signaling pathways in mediating the comorbid effects of PIC challenge on prion-related neurodegeneration.

5.3. Seizures

Intraperitoneal PIC injection also increases the vulnerability of the brain to excitotoxic insults as seen from hypersusceptibility to kainic acid (KA)-induced seizures (26, 94). This hypersusceptibility manifests as a robust increase in both the severity and protracted duration of status epilepticus as compared to saline-injected mice. The hypersusceptible phenotype lasts for three days after PIC challenge. This finding supports a causative role of peripheral viral infections in the increased seizure propensity inferred from epidemiological studies (95). A subsequent study of the hippocampus, the initial onset region for KA-induced seizures (96), revealed a robustly upregulated expression of the complement genes that was commensurate with seizure hypersusceptibility in PIC-challenged mice (33). The gene encoding complement factor B (CfB), the initiator of the alternative complement pathway featured the highest upregulation. Cerebral complement is a major modulator of neuronal activity through synaptic modification (97-99) and intracerebral injection of complement components has been shown to have a proconvulsant effect (100). Consequently, it is highly feasible that activation of the alternative complement pathway represents a mechanistic link between peripheral PIC challenge and hippocampal hyperexcitability.

In addition, the involvement of inflammatory cytokines in the induction of hyperexcitability leading to seizures is evident. For instance, IL-1β has been implicated as a major proictogenic cytokine (101, 102). IL-6 has a biphasic modality as either its over- or under-expression induces seizure hypersusceptibility (47, 48). Also, IFNβ was recently shown to mediate spontaneous interictal activity in acute hippocampal slices obtained from mice during the cytokine surge induced by peripheral PIC challenge (61).

Of note, neuronal hyperexcitability is a major contributing factor in the progression of neurodegeneration. For example, hippocampal over-activation correlates with cognitive impairment in the aging brain (103) and determines development of AD (104). As shown above, peripheral antiviral response robustly increases excitability of hippocampal circuits. Therefore, the comorbid effects of peripheral infections on neurodegeneration (85, 87-90, 105) are likely to involve hyperexcitability as a mechanistic link.

5.4. Schizophrenia and Autism

Epidemiological evidence has demonstrated a positive correlation between maternal viral infections and an increased risk of neurodevelopmental abnormalities in offspring that result in long-lasting behavioral dysfunctions in adulthood (106-108). Prenatal immune activation with PIC reproduces several features of schizophrenia and autism, and has been widely used to study these neuropsychiatric disorders (108, 109).

5.4.1. Prenatal exposure—The activation of maternal immunity with PIC has been shown to induce a range of psychopathological and neuropathological features characteristic for schizophrenia and autism. For example, PIC-challenge of pregnant dams reduces locomotor development, sensorimotor gaiting (110-114) and socialization (115) in the offspring. Other behavioral dysfunctions include cognitive deficits (110, 113, 116), depression-like behavior (116) and a reduction of EEG coherence between the dorsal hippocampus and medial prefrontal cortex (117). Other features pertaining to the neuropathology of schizophrenia and autism have also been observed in offspring exposed to maternal PIC-challenge. These include hippocampal hyperexcitability, seizure hypersusceptibility (115) and hypersensitivity to methamphetamine (110). Similar neurodevelopmental impairments were recently observed in nonhuman primates. Thus, rhesus monkeys born to females challenged with PIC during pregnancy displayed a host of behavioral abnormalities that include abnormal repetitive behavior, altered communication, atypical social interactions (118) and abnormal gaze patterns when viewing faces of unfamiliar conspecifics (119).

Morphologically, maternal PIC challenge dysregulates mouse brain development as seen from reduced proliferation of neural stem cells in the cortex (111), olfactory bulb (120) and dentate gyrus (116). Similar deficiencies in neuronal development have been observed in rats (114, 121). In rhesus monkeys, alterations of dendritic morphology of pyramidal neurons in the prefrontal cortex were recently reported (122). In addition to neuronal abnormalities, mouse offspring of PIC-challenged dams exhibited a transient decrease in axonal diameter and hypomyelination during the juvenile period (123), while microstructural alterations of the white matter within the fronto-striatal-limbic circuits persisted into adulthood (124). These findings corroborate clinical data showing a strong association of myelination defects with both schizophrenia (125) and autism (124).

At the molecular level, offspring born to PIC-challenged dams were found to feature downregulated expression of the GluN1 subunit of NMDA receptors (121), and upregulation of the metabotropic glutamate receptor 5 (mGluR5) (126), synaptobrevin (121) and choline acetyltransferase (127). The offspring also had increased tonic extracellular glutamate in the prefrontal cortex (128), impaired arginine metabolism in the hippocampus and prefrontal cortex (129) and reduced cerebral glutathione content (110).

5.4.2. Early postnatal exposure—Although important developmental events within the rodent brain occur in the early postnatal life, relatively few studies have addressed the effects of PIC challenge at this critical period. For example, repeated intraperitoneal injections of PIC during postnatal day 2-6 (P2-6) were shown to increase anxiety-like

behavior, induce sensorimotor gating deficits, as well as to impair memory and social behavior in adult mice (130). PIC challenge also exacerbated behavioral deficits in transgenic mice deficient in the disrupted-in-schizophrenia 1 (DISC1) gene (131). In rats, a single intraperitoneal injection of PIC at P14 led to robust anxiety-like behaviors assessed two month later (132). These are significant findings because schizophrenia and autism feature an anxiety component. In addition, PIC challenge to P14 rat pups was shown to alter neuroimmune responses to PIC challenge in adult rats as seen from a mitigated febrile response concurrent with an augmented corticosteroid response (133). Altogether, these studies demonstrate that the window of behavioral vulnerability to the acute antiviral response in the periphery extends well into the postnatal period.

5.5. Neuroprotection

Besides the deleterious effects of PIC challenge discussed above, the resultant inflammatory milieu may be beneficial in certain circumstances. For example, intraperitoneal administration of low doses of PIC was shown to provide protection (tolerance) from a subsequent ischemic challenge (134). The administration of PIC three days before middle cerebral artery occlusion (MCAO) profoundly reduced the infarct volume and attenuated neurological and motor deficits. Subsequent studies from the same laboratory have demonstrated that the protection is mediated by type I IFNs generated in response to PIC challenge, and that the primary mechanism entails the attenuation of ischemia-induced BBB damage (135). Importantly, post-ischemic administration of PIC also has neuroprotective effect (136). Thus, peripheral PIC challenge three hours after MCAO reduced cerebral infarct volume and edema, and improved neurological scores. Neuronal cell death and mitochondrial damage in the ischemic tissue of the PIC-challenged mice was also mitigated. These protective effects are likely mediated by decreased expression of the pro-apoptotic Bax protein and increased expression of anti-apoptotic Bcl2, Hsp27 and Hsp70 proteins. Moreover, the protection was protracted and lasted for 14 days after the onset of ischemia. The therapeutic effects of PIC challenge seem to be related to cerebral IFNβ production and to the downregulation of TLR4-mediated cascades. The neuroprotective property of PIC is intriguing in view of the overwhelming deleterious effects discussed previously. This dual activity may be related to PIC dosing. For example, the ischemic neuroprotection is only observed at PIC doses of less than 4 mg/kg (134). It seems plausible that the low doses of PIC generate neuroprotective levels of type I IFNs, while at higher doses the neuroprotective effect of IFNs is obliterated by the generation of proinflammatory mediators, e.g., TNFα and IL-1β.

6. Conclusions

The studies reviewed above demonstrate that the PIC model provides a powerful heuristic tool for studies of the immune-to-brain communication pathways at the basic neurobiological level, as well as for the delineation of mechanisms underlying comorbid effects of peripheral viral infections on neurodegeneration. The clinical significance of such studies is underscored by the fact that most neurodegenerative conditions affect the aging brain, and that viral infections become more frequent than bacterial infections in the aging population. On the other hand, maternal PIC challenge dysregulates cerebral development of

the offspring. This paradigm dovetails with the role of prenatal viral infections in the etiology of neuropsychiatric disorders. Consequently, the PIC model is well suited for the exploration of novel preventive strategies for neurodegenerative as well as neurodevelopmental disorders. Finally, there is compelling evidence that peripheral challenge with low doses of PIC may provide neuroprotection against ischemic damage. Peripherally administered PIC has been tested in clinical trials primarily as an adjuvant to anti-cancer vaccines, and has been proven to be safe even in long-term treatments. Therefore, studies employing the PIC model may lead to the development of efficient therapeutic interventions for stroke and possibly for other neuropathological conditions using PIC as a viable target drug.

Acknowledgments

This work was partly supported by a research grant from the National Institutes of Health/National Institute of General Medical Sciences, U54GM104942. The content is solely the responsibility of the author and does not necessarily represent the official views of the NIH. The author would like to thank Mr. Brent Lally for proofreading this manuscript.

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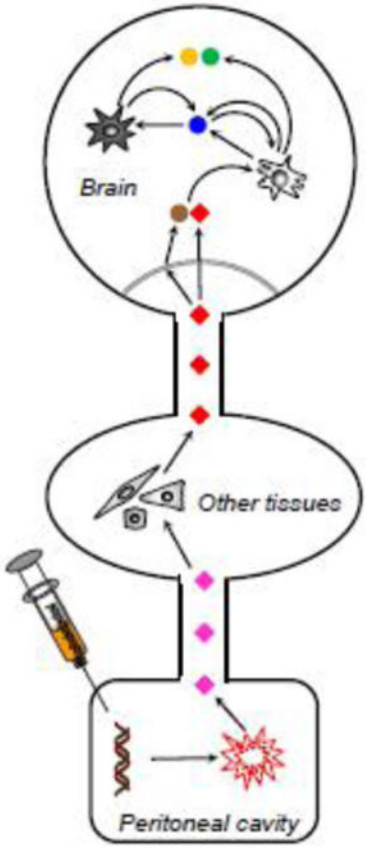

Fig. 1.

Inflammatory events in the PIC model. Intraperitoneally injected PIC elicits a fulminant response of the peritoneal macrophages and mesothelial cells leading to the generation of cytokines and other inflammatory agents (pink diamonds) that are released into the circulation. PIC itself does not reach the circulation and is rapidly degraded. The blood-borne inflammatory mediators stimulate cells in other organs, e.g., liver, muscles, to generate additional inflammatory mediators and the resulting assortment of mediators (red diamonds) reaches the brain. Some mediators gain access to the brain parenchyma via BBB of CVO (double line), while others activate the endothelial cells that release secondary mediators into the parenchyma (brown diamond). Both the peripherally-generated (transported) and endothelium-generated (transduced) agents activate resident cerebral cells (light cell) to produce additional mediators (blue circle) that can either act in an autocrine (light cell) or paracrine (dark cell) manner. Both the paracrine and autocrine stimulation may either amplify the production of the same mediator (blue circle) or induce generation of additional mediators (orange and green circles). These new mediators, in turn, may instigate paracrine/autocrine stimulation of other parenchymal cells. Altogether, these signaling cascades generate an assortment of inflammatory mediators that specifically alters the activity of neuronal circuits leading to changes in brain function. Of note, some of the cerebrally-generated mediators may enter the circulation, and thus, affect the assortment of peripherally-generated mediators. These brain-to-periphery feedback pathways would further contribute to the complexity of the cerebral response. *For specifics see the text.*

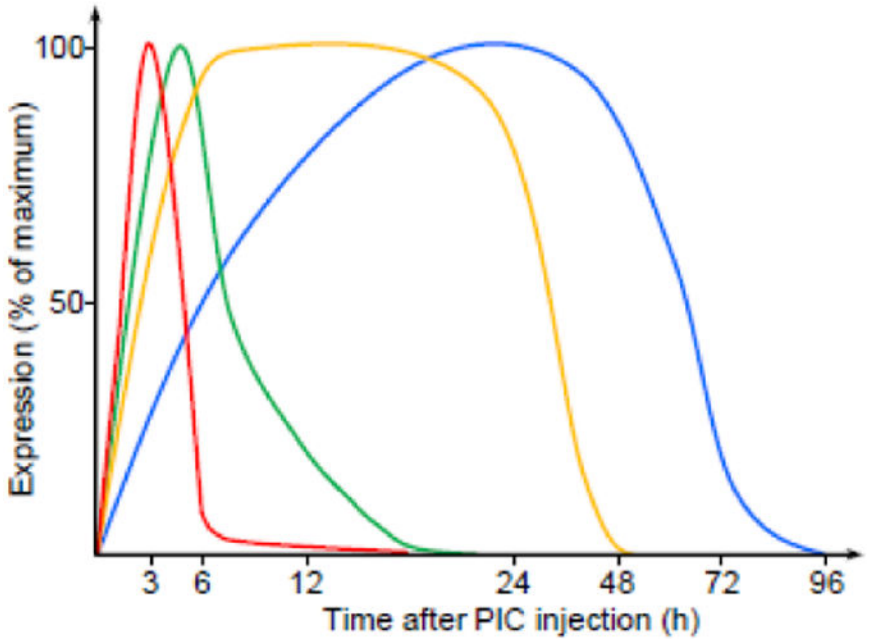

Fig. 2.

Time course of neuroinflammatory response following PIC challenge. Intraperitoneal injection of PIC elicits a robust but transient surge in blood cytokines (red), e.g., IFNβ, IL-6 and TNFα. This cytokine surge upregulates the transcription of inflammatory genes in the brain. Three major patterns of mRNA upregulation can be distinguished. Some genes, e.g., the Ifnb, Il6, Cxcl10 and Cxcl1 genes, feature a rapid upregulation that subsides by 24 h (green). Other genes, e.g., the Tnfa, Ccl7 and Ccl12 genes, are also rapidly upregulated but display a protracted course (orange). The genes encoding complement proteins, e.g., the Cfb, C3 and C2 genes, exhibit more gradual upregulation that lasts for three days (blue). Generalized from (23, 26, 27, 31, 33).