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Neuroinflammation and Memory: The Role of Prostaglandins

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Abstract Neuroinflammation is a complex response to brain injury involving the activation of glia, release of inflammatory mediators within the brain, and recruitment of peripheral immune cells. Interestingly, memory deficits have been observed following many inflammatory states including infection, traumatic brain injury (TBI), normal aging, and Alzheimer's disease (AD). Prostaglandins (PGs), a class of lipid mediators which can have inflammatory actions, are upregulated by these inflammatory challenges and can impair memory. In this paper, we critically review the success of nonsteroidal anti-inflammatory drugs, which prevent the formation of PGs, in preventing neuroinflammation-induced memory deficits following lipopolysaccharide injection, TBI, aging, and experimental models of AD in rodents and propose a mechanism by which PGs could disrupt memory formation.

Keywords Neuroinflammation · Prostaglandins · Learning · Memory · Hippocampus · Cyclooxygenase · NSAID · Lipopolysaccharide · Traumatic brain injury · Aging · Alzheimer's disease

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Introduction

Many neuroinflammatory conditions are associated with cognitive dysfunction. Patients suffering from traumatic brain injury (TBI) or stroke often have substantial memory deficits for weeks or months following their trauma [1, 2]. Similarly, elevated levels of pro-inflammatory cytokines and prostanoids, indicative of neuroinflammation, are found in patients with Alzheimer's disease (AD) and AIDS-related dementia, two additional disorders characterized by profound cognitive decline [3–5]. Despite the increasingly large population affected by these conditions, few if any therapies exist to improve memory in these neuroinflammatory states. Clearly, there is a great need to understand how neuroinflammation can impair memory processes and, in particular, to identify the key molecules involved and how they can be therapeutically targeted to prevent cognitive dysfunction.

Neuroinflammation

Neuroinflammation is defined as the activation of the brain's innate immune system in response to an inflammatory challenge and is characterized by a host of cellular and molecular changes within the brain. Glial cells, most notably astrocytes and microglia, become activated. Their processes become hypertrophied, they upregulate cell-surface immune modulatory proteins, and they increase the synthesis and release of pro-inflammatory molecules including cytokines, chemokines, and prostanoids. Neuroinflammation is often also accompanied by disruption of the blood–brain barrier and increased numbers of infiltrating leukocytes. Depending on the brain regions affected, these cellular and molecular changes can lead to sickness response behaviors including fever, anhedonia, hypophagia,

hypersomnia, hyperalgesia, reduced social behaviors, and cognitive deficits [6]. These sickness response behaviors are not simply a result of decreased energy, but rather represent an active response that is aimed at enhanced recovery and increased survival [6].

The exact pattern of cellular, molecular, and behavioral changes depend largely on the type and duration of the inflammatory challenge experienced by the organism. Neuroinflammation can result from classical injuries such as direct insult to the brain that occurs with TBI, encephalitis, or ischemia or from peripheral insults such as infection that follows exposure to bacteria. However, neuroinflammation also occurs following less traditional injuries such as neurodegenerative disorders and even with normal aging and exposure to certain stressors.

In the case of direct brain insult such as TBI, glial cells, particularly astrocytes and microglia, become activated and secrete pro-inflammatory molecules within the brain. In contrast, peripheral insults first activate local, peripheral immune cells to release cytokines into the circulation which then signal the brain to induce neuroinflammation via multiple routes. Circulating cytokines have low diffusion across the blood–brain barrier but can enter the brain at circumventricular organs, which lack a blood–brain barrier [7]. Alternatively, these inflammatory mediators may activate vascular endothelial cells and stimulate the release of neuroinflammatory prostaglandins (PGs) within the brain parenchyma. Specific carriers for certain cytokines also exist along the blood–brain barrier to facilitate saturable transport into the brain [8]. Finally, activation of vagal nerve afferents by peripheral cytokines induces de novo synthesis and release of inflammatory molecules within the brain parenchyma [9, 10] (see [11] for review).

Regardless of the route of stimulation, activated brain glial cells can upregulate and secrete pro-inflammatory molecules including cytokines, chemokines, and prostanoids, within the brain parenchyma. Interleukin-1 (IL-1) is a powerful pro-inflammatory cytokine with pleiotropic physiological and behavioral functions. Elevated IL-1 activates glia, increases blood–brain barrier permeability, causes leukocyte infiltration, induces its own expression, and upregulates other pro-inflammatory molecules including PGs [12–15]. Elevated IL-1 also is sufficient to induce sickness response behaviors including fever, anhedonia, hypophagia, reduced social behaviors, and cognitive deficits [16–20].

Neuroinflammation and Memory

Interestingly, a number of cognitive disorders including AD and AIDS-related dementia are associated with elevated brain levels of proinflammatory molecules including IL-1 and PGs [3, 5, 21, 22]. This observation suggested a possible link between elevated proinflammatory molecules and memory dysfunction in humans. Moreover, numerous animal studies have found a causative link between elevated IL-1β levels and memory deficits resulting from neuroinflammation [23–27]. Inflammatory conditions that elevate brain levels of IL-1 such as infection or stress impair memory and pharmacologically inhibiting IL-1 prevents these deficits [20, 24, 25, 28]. Peripheral as well as direct intracerebral injection of IL-1β and chronic hippocampal IL-1β overexpression also impair long-term memory [19, 20, 23, 26, 29]. These studies demonstrate that IL-1β is necessary and sufficient to cause memory deficits in certain neuroinflammatory conditions. The detrimental role of IL-1β on learning and memory processes has been reviewed further elsewhere [30].

The mechanism by which neuroinflammation and, in particular, elevated IL-1 impair memory is largely unknown. Neuroinflammatory mediators such as IL-1β, tumor necrosis factor alpha (TNFα), and nitric oxide can induce the production of PGs via cyclooxygenase (COX), the rate-limiting enzyme in this pathway [13, 31, 32]. Circulating IL-1β, which has low diffusion across the blood–brain barrier, has been shown to upregulate COX mRNA within brain vascular endothelium causing the release of PGs into the brain parenchyma. IL-1β within the brain can also cause the release of PGs from glial cells [13]. Thus, PGs are in a position to mediate some of the effects of neuroinflammation and IL-1β within the brain. Consistent with this possibility, PGs have been shown to mediate several behavioral responses to elevated IL-1β, including fever, hypophagia, depressive-like behavior, and reduced social exploration [33–38].

The foregoing suggests that PGs may be downstream mediators of the impact of neuroinflammation and IL-1β on memory processes. In this review, we will examine the possibility that PGs are responsible for memory deficits in varied neuroinflammatory conditions. Therefore, we will (1) briefly review the role of PGs in neuroinflammation, (2) extensively review the detrimental role of elevated PGs on memory following lipopolysaccharide (LPS), TBI, and aging, as well as in models of AD, and (3) hypothesize a potential mechanism for the memory impairing effect of PGs. Many of these studies use nonsteroidal anti-inflammatory drugs (NSAIDs), whose primary anti-inflammatory action is to inhibit COX activity thereby reducing the production of PGs.

Memory Tasks

In this paper, we will review studies utilizing a wide array of different learning and memory tasks. The Morris water maze (MWM), which was developed 25 years ago, is the most extensively used memory test [39]. In the MWM, an

animal must swim in a tank to find a hidden platform. The animals receive multiple training trials per day for numerous days. At the end of training, a probe trial is often used, where the platform is removed and the search pattern is monitored for a short period of time. Dependent measures can include time in target quadrant, latency to target quadrant, and platform crossings (swimming over the location where the platform used to reside). Researchers can also run a visible trial, where the platform is made visible by a conspicuous object. Data from this trial helps to control for potential differences in swimming speed or motivation between experimental groups. In the MWM, the animal is motivated by its intrinsic dislike of water. Therefore, results from this test depend greatly on treatments that affect motor performance and anxiety or motivational states. These parameters should be considered in analyzing data obtained from this task.

Contextual fear conditioning is another widely used memory test. There are two phases to this paradigm: conditioning and testing. During conditioning, an animal is placed in a novel context and explores and learns the features that comprise this context. After a few minutes, one or a series of shocks are delivered through a floor grid. During the testing phase, the animal is re-exposed to the conditioned context, and the amount of time spent freezing is measured. Freezing is a robust fear response in rodents and is a measure of learning in this task. If the animal formed a strong representation of the context during conditioning, it will display a high level of freezing to the context. Additionally, a tone can be added before the shock in the conditioning phase. The animal's freezing to the tone in a novel context then can be tested. Memory for the context depends on the hippocampus, while memory for the tone does not, allowing two different types of memory to be tested in the same task [40].

To describe in detail here the nine other tasks used in the papers reviewed would be unwieldy. Therefore, for each study, we will note the task used and the type of memory tested, e.g., working, short-term, or long-term memory. We also direct readers not familiar with hippocampal memory tasks to other reviews that describe in detail many of the tests used [41–43].

Caveats

In this review, we will restrict our discussion to the role of elevated PGE_2 in hippocampal-dependent memory impairments. However, basal, physiological levels of PGs are also necessary for normal LTP and memory [44]. These findings taken together suggest a hormetic or inverted U-shaped relationship for PGs and memory, where reductions below and elevations above basal levels impair normal memory. It should be noted that the same relationship has been found for IL-1 and memory, further linking these pro-inflammatory molecules in their impact on memory [45]. Researchers have extensively studied this physiologic role of PGs, but we will not review these studies here [44, 46–50]. Furthermore, other PGs in addition to PGE_2 may negatively affect learning and memory. Studies inhibiting COX with NSAIDs do not distinguish between the effects of different PGs. However, direct application studies show a clear role of elevated PGE_2 in impairing memory. Therefore, we will restrict our discussion to PGE_2 but do not rule out a role for other PGs. Finally, neuroinflammation likely impairs many types of learning and memory [51]; however, the greatest area of research is on hippocampal-dependent memory, so we will focus our review on the role of PGs in hippocampal-dependent memory.

This review is aimed at elucidating the role of elevated PGs in hippocampal-dependent memory deficits and suggests that PGs may be responsible for the negative effects of IL-1 on memory, as well. However, many other inflammatory and hormonal systems are also affected by the treatments discussed below. For example, IL-1 also increases levels of IL-6 and TNFα, molecules which some researchers hypothesize are critical for neuroinflammation-induced memory deficits [12, 52–54]. Similarly, levels of cortisol in humans or corticosterone in animals are elevated by IL-1, and some research suggests that these hormones may impair memory [55, 56]. Because these inflammatory and hormonal systems are interrelated and regulated by each other, it is difficult to distinguish the function of these individual molecules. Therefore, we will restrict our discussion to the role of NSAIDs and PGs. However, we will note levels of additional inflammatory and hormonal molecules when they are examined and do not discount a potential role for these molecules in neuroinflammation-induced memory deficits.

Neurobiology of Prostaglandins

In order for PGs to be responsible for disrupting memory in neuroinflammatory states, several conditions must be met: (1) PGs must be elevated with inflammation in brain regions responsible for memory, most notably within the hippocampus, (2) PGs must be increased and receptors present at specific plasticity sites, e.g., neuronally, either at pre- or postsynaptic sites, (3) conditions that increase PGs within the hippocampus or direct application of PGs should impair memory, and COX inhibition should prevent deficits from the former, and (4) a mechanism should exist by which PGs could impair learning and memory processes. In the following sections, we will demonstrate that all four conditions are met for PGE_2.

PGs are a class of eicosanoids that are formed by the liberation of arachidonic acid from phospholipids and a two-step conversion by COX enzymes (Fig. 1). COX enzymes are the rate-limiting enzymes in the formation of PGs; therefore, their regulation is crucial in the control of PG synthesis. Two main isoforms of the COX enzyme exist, COX-1 and -2, which show 60% homology within a species [57, 58]. COX-1 is traditionally thought to have constitutive expression, while COX-2 is highly inducible, although this distinction is not as apparent within the brain. In fact, COX-2 has high basal expression within the brain and particularly the hippocampus, while COX-1 mRNA and protein are increased in the hippocampus by inflammatory stimuli [59]. A third isoform, COX-3 or COX-1b, has also been described. COX-3 is a splice variant of COX-1, having an identical sequence except for the inclusion of intron 1 [60, 61]. COX-3 transcript is expressed in murine brain homogenates and cultured astrocytes and microglia, although its expression is not increased by acute IL-1β treatment [60]. The predicted amino acid sequence of COX-3 in mouse has little homology to the COX-1 or -2 protein and is unlikely to have COX activity needed to produce PGs [62]. Therefore, in considering the role of PGs and COX in neuroinflammation, we will focus on COX-1 and -2 isoforms.

PGs are released by neuronal and glial cells in response to inflammatory challenge. For example, peripheral LPS injection up-regulates expression of COX-2 in endothelial cells within the brain vasculature [63]. PGE_2 once released can readily cross the blood–brain barrier. PGE_2 has a short half-life and, therefore, acts in a paracrine or autocrine fashion. Elevations in PGE_2 and COX have been found within the hippocampus following LPS injection, TBI, aging, and IL-1β injection [26, 63–65]. Therefore, neuroinflammatory conditions do elevate PGs within the hippocampus, a brain structure critical for many forms of memory.

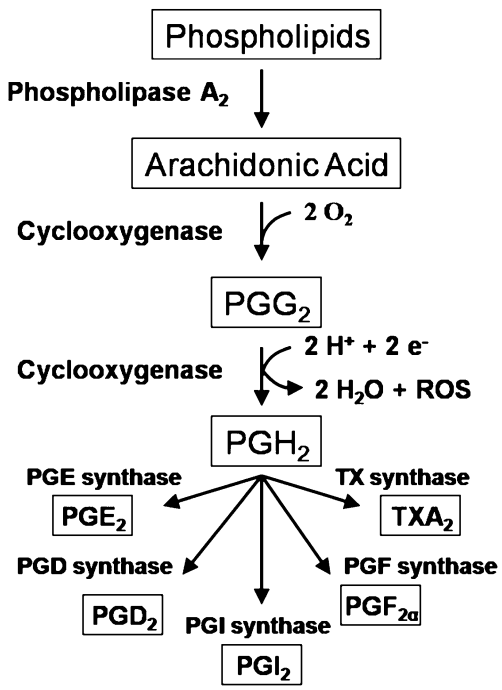

Fig. 1 Prostaglandin synthesis

PGE_2 exerts its actions by binding to EP receptors (EPRs) of which there are four known subtypes, 1–4, in the rat brain. Binding of PGE_2 to these G protein-coupled receptors leads to activation of different signaling pathways. Activation of the EP1 receptor induces calcium mobilization, and EP2 and EP4 are linked to Gs molecules mediating a rise in intracellular cAMP. Conversely, activation of the EP3 receptor reduces cAMP through Gi signaling and is therefore termed the "inhibitory" receptor, though several splice variants are expressed that may be coupled to other second messenger effects. Of these EP receptors, EP3 has the highest affinity for PGE_2 and is most abundantly expressed within the brain [66, 67]. Within the hippocampus, EP2 and EP3 receptors show the highest expression levels with EP2 receptors being primarily presynaptic and EP3 receptors postsynaptic [66, 68]. Therefore, PGE_2 is able to exert its effects in sites critical to synaptic plasticity mechanisms, notably at pre- or postsynaptic dendritic sites.

The following sections will evaluate the ability of elevated PGs to impair memory, COX inhibitors to prevent this impairment, and possible mechanisms that could explain this effect. The role of PGs in neuroinflammation-induced memory deficits caused by LPS injection, TBI, aging, and AD will be examined in detail (summarized in Table 1). Finally, the role of elevated PGs in LTP studies will be reviewed, and possible mechanisms by which binding of PGE_2 to its EP3R may impair memory discussed.

Prostaglandins and Memory

Physiological Elevations in Prostaglandins

Lipopolysaccharide

Peripheral injection of LPS is commonly used to study infection and is known to induce neuroinflammation. Although active, replicating bacteria is not administered, the animal's immune system recognizes pathogen-associated molecular patterns and stimulates an immediate and robust immune response. IL-1β mRNA is elevated within the hippocampus within 2 h after LPS injection, and by 5 h and for up to 24 h after injection IL-1β protein is increased [69, 70]. Following peripheral LPS injection,

Table 1 Summary of reviewed studies examining the detrimental role of elevated PGs in memory function following a variety of neuroinflammatory states

Inflammatory challenge and NSAID	Dose/Route/Duration of NSAID	Memory task	Effect on memory	Ref
Lipopolysaccharide				
NO-flurbiprofen	15 mg/kg s.c. for 28 days	MWM	Improved	[74]
Rofecoxib	1.92 mg/kg p.o. for 7 days	Passive avoidance and elevated plus maze	Improved	[71]
Dexiprofen	50 mg/kg s.c. for 28 days	Delayed matching-to-place and MWM	Improved	[75]
Indomethacin	10 mg/kg i.p. for 7 days	Active avoidance	Improved	[73]
Ibuprofen	30 mg/kg i.p.	MWM	Improved	[72]
Traumatic brain injury				
Nimesulide	6 mg/kg i.p. for 10 days	Barnes circular maze	Improved	[76]
Celecoxib	50 mg/kg p.o. 2×/days for 5 days	MWM	No change	[77]
DFU	1 or 10 mg/kg i.p. 2×/days for 3 days	MWM	Improved with high but not low dose	[64]
Aging				
Celecoxib	3 mg/kg p.o. 2×/days for 4 m	MWM	Improved	[65]
Naproxen	6.82 mg/kg		Improved	[71]
Nimesulide	2.42 mg/kg		Improved	[71]
Rofecoxib	1.92 mg/kg p.o. for 15 days	Passive avoidance and elevated plus maze	Improved	[71]
Sulindac	500 ppm for 2 m	RAWM and contextual fear conditioning	Improved	[79]
Models of Alzheimer's disease				
NS-398	5 mg/kg i.p. for 4 days	Object recognition	Improved	[82]
Mefenamic acid	5 mg/kg i.p. for 3 weeks	MWM	Improved	[81]
Ibuprofen	375 ppm for 4 weeks	MWM	Improved	[86]
Naproxen	375 ppm for 4 weeks	MWM	Improved	[86]
MF tricyclic	13 ppm for 4 weeks	MWM	Improved	[86]
Ibuprofen	375 ppm for 4 m	Forced choice alternation (T maze)	Improved	[86]
		MWM	Improved	[86]
Celecoxib	1,500 ppm for 3.5–4 m	3-trial Y maze	Improved	[89]
Ibuprofen	375 ppm for 5 m	MWM	Improved	[92]
hCOX-2 overexpression		MWM, active avoidance, and inhibitory avoidance	Impaired in older, but not younger mice	[95]
IL-1β				
Diclofenac	3.2 or 10 mg/kg s.c.	3-panel runway task	Improved at high but not low dose	[94]
Naproxen	1 μg intra-hippocampally	Contextual fear conditioning	Improved	[26]
PGE_2	0.01, 0.1, or 1 μg/side intra-hippocampally	3-panel runway task	Impaired	[94]
PGE_2	250 or 500 ng/side/h intra-hippocampally for 6 h	Contextual fear conditioning	Impaired	[26]

COX-2 immunoreactivity and PGE_2 are also increased within the hippocampus along with other pro-inflammatory molecules [63]. Sickness behaviors including fever, suppression of social interaction, and hypophagia can continue for 1–2 days after administration. Additionally, cognitive impairments have been reported by numerous groups when animals are trained immediately before or at short intervals after LPS injection. Experiments with LPS injections occurring after training provide particularly strong evidence that LPS-induced inflammation interferes with memory consolidation per se and not some nonspecific function such as attention, sensation, or motor performance.

Using this model of sickness and neuroinflammation, researchers have shown that elevated PGs are necessary for LPS-induced memory deficits. Jain et al. [71] injected mice with LPS (50 μg/mouse intraperitoneally, i.p.) immediately

after training in passive avoidance and an elevated plus maze, both hippocampal-dependent tasks. A COX-2 selective inhibitor (rofecoxib, 1.92 mg/kg orally, p.o.) was administered for 7 days beginning immediately after the LPS injection. LPS had no effect on general motor performance but significantly impaired memory at 1 and 7 days after injection in both tasks. Treatment with the COX-2 selective inhibitor completely reversed these deficits and restored normal learning and memory. In a different experiment, LPS injection (250 μg/kg i.p.) 4 h before training in the MWM caused rats to spend less time on a direct path to the hidden platform [72]. These results indicate spatial deficits in LPS-injected rats. When a nonselective COX inhibitor (ibuprofen, 30 mg/kg i.p.) was given 1 h before LPS, LPS-induced spatial memory impairments were completely prevented. Both of these studies demonstrate that physiologically elevated PGs, which are produced from COX activity, are necessary for memory deficits that result from peripheral LPS injection.

In contrast to peripheral administration of LPS leading to neuroinflammation, LPS can be injected into specific brain regions, such as the hippocampus, to cause neuroinflammation directly. This manipulation examines specific effects of local hippocampal neuroinflammation on learning and memory, reducing some of the potential peripheral or non-hippocampal effects. Bilateral, intra-hippocampal LPS injections (1 μg/side) impaired acquisition and retention in an active avoidance task in rats [73]. However, daily administration of a nonselective COX inhibitor (indomethacin, 10 mg/kg i.p.) for 7 days enhanced performance in LPS-treated rats, especially by improving long-term memory for the retention trial. Therefore, reducing physiologically elevated PGs with a nonselective COX inhibitor improves memory following acute intra-hippocampal LPS injections.

Some researchers have become interested in the effects of not just acute, but chronic neuroinflammation, similar to what might be seen in neurodegenerative diseases such as AD. One way to create chronic neuroinflammation is by infusing LPS into the brain for a prolonged time. The Wenk group has extensively studied such a model by chronically infusing LPS into the fourth ventricle for 28 days through a cannula attached to an osmotic mini-pump. Hauss-Wegrzyniak et al. [74] showed that chronic neuroinflammation resulting from 28 days of intraventricular LPS (.25 μg/h) impaired performance in the MWM. Daily subcutaneous (s.c.) injections of a novel NSAID without gastrointestinal side effects (NO-flurbiprofen, 15 mg/kg) for the length of the LPS infusions improved spatial performance, returning latencies to find the hidden platform to control levels. Using the same model, Jin et al. [75] found that chronic intraventricular LPS impaired retention but not learning in a delayed matching-to-place version of the MWM that tests working memory. Again, daily nonselective COX inhibition (dexiprofen, 50 mg/kg subcutaneously, s.c.) prevented these deficits. Together, these reviewed studies demonstrate that both peripheral and central as well as acute and chronic LPS treatments impair memory. More to the point, reducing physiologically elevated PGs by treatment with nonselective and COX-2 selective inhibitors can prevent these memory deficits.

Traumatic Brain Injury

Neuroinflammation can arise from insults other than classic infection. Models of TBI result in chronic neuroinflammation with clear clinical implications. Cernak et al. [76] used the 2-m impact acceleration model of diffuse TBI to examine the role of PGs in resulting memory deficits. In this model, hippocampal COX-2 protein was maximally increased from 1 to 3 days after injury and remained elevated 12 days after injury (last time point examined). Rats' hippocampal-dependent spatial reference memory was tested in the Barnes circular maze daily for 10 days following TBI. Animals were injected with a COX-2 selective inhibitor (nimesulide, 6 mg/kg i.p.) or vehicle beginning 30 min after TBI and continuing daily for 10 days. TBI rats had impaired performance in the maze, and COX-2 inhibition improved this deficit at 1 and 2 days as well as 7 and 8 days after TBI. COX-2 inhibition also improved general motor performance, but this improvement was only significant 1 day after TBI. Therefore, COX-2 inhibition appears to improve spatial memory in rats following diffuse TBI.

Using the lateral cortical impact model of TBI, a different group found similar results in the MWM. Twice daily dosing of a selective COX-2 inhibitor [5,5-dimethyl-3 (3-fluorophenyl)-4(4-methylsulfonyl)phenyl-2(5H)-furanone (DFU), 1 or 10 mg/kg i.p.] for 3 days after TBI improved performance in probe trials of the MWM at high, but not low doses [64]. Interestingly, Gopez et al. [64] show that a low dose of DFU (1 mg/kg) administered 10 min before TBI is sufficient to attenuate the increase in hippocampal PGE_2, despite its inability to improve memory at this dose whether administered before or after TBI. Whether further inhibition of PGE_2 production by the higher dose of DFU is needed or nonspecific side effects of COX-2 inhibition are responsible for the beneficial effects seen on memory with the higher dose is unknown. COX-2 inhibition did not affect swim speed or beam walk performance. These studies suggest that COX-2 inhibition improves spatial hippocampal-dependent memory following neuroinflammation caused by multiple types of TBI.

Despite these positive findings that are in agreement with the LPS results discussed above, not all published studies of TBI in animals have found beneficial effects of

NSAIDs on cognitive function. Dash et al. [77] also examined molecular and behavioral changes in rats after lateral cortical impact injury and treatment with a COX-2 selective inhibitor (celecoxib, 50 mg/kg p.o. twice daily on days 1–4 post-injury). COX-2 immunoreactivity was increased in the hippocampus at 3 h and up to 3 days after TBI. Motor function was assessed pre-injury and for the following 4 days during drug treatment and, surprisingly, COX-2 inhibition worsened motor function. Memory was tested 3 days after the last motor test, and COX-2 inhibition had no effect on memory in the MWM or contextual and auditory fear conditioning. It should be noted that no sham group without TBI was included in these memory tests. Seven days after TBI, memory may no longer be impaired in these animals, and a lack of a beneficial effect of COX-2 inhibition would not be surprising. Also, halting drug treatment 2 days before memory testing may have allowed PG levels and inflammation to increase. Therefore, strong conclusions cannot be drawn from the lack of benefit on memory from COX-2 inhibition. Nevertheless, although some COX-2 selective inhibitors have proven beneficial in improving memory deficits in certain models of TBI, COX-2 inhibitors may not be universally beneficial following TBI. The model of TBI, type of COX inhibitor, dose of drug, and duration/timing of dosing may all be critical to determining the success of NSAIDs in improving cognitive outcome following TBI.

Aging

External, experimenter manipulation is not always required to attain neuroinflammation. Normal aging is often associated with increased neuroinflammation as measured by elevated IL-1β, PGE_2, MHCII, etc., especially within the hippocampus [65, 78, 79]. Hippocampal-dependent memory impairments are often concomitant with this neuroinflammation. A number of researchers have examined this relationship and have shown elevated PGs to be necessary for these memory impairments. Jain et al. [71] found memory deficits in aged (16 months old) compared to young (3 months old) mice in both a passive avoidance task and an elevated plus maze. When nonselective (naproxen, 6.82 mg/kg), COX-2 preferential (nimesulide, 2.42 mg/kg), and COX-2 selective (rofecoxib, 1.92 mg/kg p.o.) inhibitors were administered for 15 days before training, these memory deficits in aged animals were prevented. COX inhibition did not affect total activity but did improve sensorimotor performance as measured by the rota-rod test in aged animals. These results were replicated for the preferential COX-2 inhibitor in a separate paper by the same group in 2005 [80]. Once again, aging impaired memory in the elevated plus maze and 15 days of treatment with a COX-2 preferential inhibitor improved performance in this task as well as improving sensorimotor performance. These experiments suggest that nonselective and COX-2 selective inhibition improve hippocampal-dependent memory in aged mice. However, given that COX inhibition also improves sensorimotor performance in these aged mice, a skill that is potentially useful in these memory tasks, it is important to tease out this confound in future studies.

Other aging studies examining the role of neuroinflammation in memory have used chronic dosing of NSAIDs. For example, Mesches et al. [79] administered a nonselective COX inhibitor [sulindac, 500 parts per million (ppm)] in the food of young (6 months) and aged (18 months) rats for 2 months before training. Animals were then trained in the radial arm water maze (RAWM) followed by contextual fear conditioning, both hippocampal-dependent tasks. Aged animals showed spatial working memory deficits in the RAWM and long-term memory deficits in contextual (hippocampal-dependent) but not auditory (hippocampal-independent) fear conditioning. PG levels themselves were not measured in this study, but 2 months of COX inhibition did reduce hippocampal IL-1β protein levels in aged animals, returning them to levels seen in young animals. Similarly, Casolini et al. [65] found age-related memory deficits in the MWM. Three- 16- and 22-month-old rats were trained in the MWM after 4 months of COX-2 selective inhibition (celecoxib, 3 mg/kg twice daily p.o.; only 15 days of control treatment for the 3-month group). Oddly, the group aged 22 months did not differ from the young animals, while the group aged 16 months was significantly impaired. Four months of COX-2 selective inhibition returned performance in the 16-month-old rats to levels seen in the young animals. Within the hippocampus, levels of IL-1β, TNFα, and PGE_2 as well as plasma corticosterone levels were elevated in both 16 and 22 compared to 3-month-old animals. COX-2 inhibition also significantly reduced IL-1β, TNFα, PGE_2, and corticosterone levels in 16 but not 22-month-old rats, although levels in aged COX-2-treated animals did not return to those seen in young animals. Anxiety-like behavior was measured in the elevated plus maze with aged animals showing increased anxiety, which was prevented in 16-month-old animals by treatment with the COX-2 selective inhibitor. The animal's level of motivation in the MWM is critical to the success of the task. Anxiety may affect this aspect independent of effects on memory; therefore, this potential confound should be considered in examining these results. Nevertheless, these data show that chronic COX inhibition can prevent aging-induced memory deficits, potentially by reducing levels of pro-inflammatory molecules within the brain. This last study also suggests that a critical time window may exist for intervention with NSAIDs. Administration after a certain age (e.g., 18 months) may no longer have beneficial effects on memory.

Models of Alzheimer's Disease

In addition to normal aging, AD is another condition associated with both neuroinflammation and cognitive impairments. Modeling the human condition of AD in rodents has proven difficult and, therefore, multiple models have been developed that mimic different aspects of the disease. Here we will examine four different models: (1) injection of amyloid β peptide into the brain (acutely or chronically), (2) Tg2576, which overexpress a Swedish mutation of the human amyloid precursor protein (APP), (3) a double transgenic (Tg) mouse expressing mutant forms of APP_{swe} and presenilin 1 (PS1), and (4) a triple Tg mouse overexpressing human APP_{swe}, $PS1_{M146V}$, and tau_{P301L}. We will review the ability of different NSAIDs to prevent hippocampal-dependent memory deficits in these models.

Amyloid β plaques within the brain are a hallmark pathological sign of AD. Rodents do not naturally form these plaques. Therefore, to experimentally study the effects of Aβ on the brain in vivo, researchers inject Aβ into the rodent brain and observe subsequent behavioral changes. For example, Joo et al. [81] infused $Aβ_{1-42}$ (600 pmol/day) or vehicle into the lateral ventricle of rats continuously for 1 week followed by 3 weeks of treatment with a nonselective COX inhibitor (mefenamic acid, 5 mg/kg/day i.p.). $Aβ_{1-42}$-infused rats were impaired in the MWM probe test, indicating impaired spatial memory. Three prior weeks of COX inhibition prevented this deficit in the MWM. In a different model, 12-month-old mice were injected intracerebroventricularly with Aβ (1 nmol) or vehicle and then with LPS (1 mg/kg i.p.) or vehicle [82]. Aβ-LPS-injected mice then received injections of a COX-2 inhibitor (NS-398 5 mg/kg i.p.) for 4 days. Seven days after Aβ injection, Aβ-LPS-injected mice showed large deficits in object recognition compared to control animals and Aβ injected animals showed an intermediate level of memory (Aβ impaired from control, Aβ-LPS impaired from Aβ). COX-2 inhibition improved memory in Aβ-LPS-injected animals to levels seen in animals injected with Aβ alone. Unfortunately, a group injected with Aβ alone and the NSAID was not included. Therefore, we cannot conclude in this model whether COX inhibition improved memory from Aβ injection, LPS, or both. Nevertheless, in these studies with Aβ-injected rodents, COX inhibition did improve memory function.

The APP_{swe} overexpressing Tg2576 mice have been well studied. Aβ levels become abnormal by ~6 months of age although plaques do not develop until 11–13 months of age [83, 84]. Tg2576 mice show hippocampal-dependent memory deficits by 6–9 months, and a recent study showed NSAIDs to be effective in improving memory in these Tg mice [84–86]. Kotilinek et al. [86] used two nonselective COX inhibitors (ibuprofen or naproxen, 375 ppm) and one COX-2-selective inhibitor (MF tricyclic, 13 ppm) to try to prevent memory deficits in the APP_{swe} overexpressing Tg2576 mice. Doses of NSAIDs were carefully selected to mimic low to moderate human doses, and to ensure the primary action of the drug was to inhibit COX. NSAID treatment was started at 11.5 months of age and continued for 4 weeks before MWM training began. Transgenic mice were significantly impaired across the training trials and during probe tests. All NSAID-treated groups had a faster rate of learning and improved long-term memory, similar to learning seen in the wild-type controls. No differences in swimming speed were found. In a second experiment, Tg2576 mice were treated preventatively with a nonselective COX inhibitor (ibuprofen, 375 ppm) beginning at 4.5 months of age and continuing for 4 months. Mice were tested for spatial working memory in the T maze (forced choice alternation) and spatial reference memory in the MWM. Tg2576 mice showed impaired performance, and preventative treatment with a nonselective COX inhibitor significantly improved performance in both tasks. Elevated brain levels of TNFα and IL-1β were found at 13 months in Tg compared to wild-type controls. Treatment with all three NSAIDs significantly lowered IL-1β levels. However, 13-month-old NSAID-treated animals with normal memory still had significantly elevated IL-1β compared to 10.5-month-old Tg mice with memory deficits, indicating a dissociation between brain IL-1β and memory. Forebrain levels of $Aβ_{40}$, $Aβ_{42}$, $Aβ_{56}$, and APP did not change with NSAID treatment, indicating that the beneficial effect of NSAIDs on memory was not due to lowered Aβ load. Finally, COX-2 mRNA levels did not differ in the hippocampus and frontal cortex between Tg and wild-type mice. PGE_2 levels were actually lower in Tg compared to wild-type mice, and COX inhibition did not significantly affect total levels. In order to try to correlate memory performance in Tg2576 mice to levels of pro-inflammatory molecules, Tg mice were grouped into low-, medium-, and high-performing bins based on performance in the MWM. Brain PGE_2 levels in NSAID-treated animals showed a significant inverse correlation with performance in the MWM, while TNFα, IL-1β, total $Aβ_{40}$, and total $Aβ_{42}$ did not correlate. NSAID-treated Tg2576 mice with high forebrain PGE_2 performed worse in the MWM, while those with low PGE_2 performed well. Therefore, nonselective and COX-2-selective inhibitors are successful in preventing working and long-term memory deficits in APP_{swe}-overexpressing mice. The beneficial effects of NSAIDs in these studies appear to be due to their ability to reduce brain levels of PGE_2 and not other anti-inflammatory or Aβ-lowering effects [86].

The APP_{swe}/PS1dE9 double transgenic mouse model of AD shows accelerated amyloid deposition compared with

the single transgenic Tg2576 mice [87]. These double transgenic mice have impairments in LTP and working memory in the RAWM by 3 months of age but do not develop long-term memory impairments in the MWM until 6–8 months of age [88]. Melnikova et al. [89] examined the interaction of human COX-2 overexpression in the APP_{swe}/PS1dE9 Tg mouse model of AD. They found that trigenic animals with the APP_{swe}/PS1dE9 mutations and COX-2 overexpression showed a fourfold elevation in brain PGE_2. Treatment with the COX-2 selective inhibitor, celecoxib, for 3.5–4 months reduced this PGE_2 increase. In behavioral tests, Melnikova et al. [89] found that female but not male trigenic mice were impaired in working memory in the three-trial Y maze compared to APP_{swe}/PS1dE9 mice without the COX-2 Tg, and these deficits could not be explained by differences in motor activity. No deficits were found in APP_{swe}/PS1dE9 Tg mice compared to WT or in either gender in long-term memory in this task. Selective COX-2 inhibition for 3.5 months reversed the working memory deficit in female trigenic mice. COX-2 inhibition had no significant effect on amyloid plaque deposition, $A\beta_{40}$, or $A\beta_{42}$ (although $p<0.07$ for reducing $A\beta_{42}$), suggesting that the beneficial effect of COX-2 inhibition was not due to effects on amyloid deposition. They also showed that COX-2 inhibition had no effect on $A\beta_{40}$ or $A\beta_{42}$ levels in APP_{swe}/PS1dE9 Tg mice crossed with a different COX-2 Tg model, which shows a high COX-2 overexpression and 25-fold elevation in PGE_2 [89]. These results support those of Kotilinek et al. [86] and suggest that the memory-enhancing effect of chronic COX inhibition in models of AD is independent from changes in amyloid plaque deposition or Aβ.

The triple transgenic (3× Tg) mouse model of AD developed by LaFerla in 2003 differs from the previous two models in its development of tau pathology and tangles along with Aβ plaques [90]. Intracellular $A\beta_{42}$ accumulation develops early in this model around 4 months of age in the cortex and 6 months of age in the hippocampus followed by the development of extracellular Aβ deposits, tau pathology, and tangles [91]. McKee et al. [92] assessed the ability of a nonselective COX inhibitor to prevent hippocampal-dependent memory deficits in these mice. Mice were treated with vehicle or a nonselective COX inhibitor (ibuprofen, 375 ppm) from 1–5 months of age and then trained in the MWM. Untreated 3× Tg mice were unable to learn the location of the hidden platform over 7 days of training. Tg mice treated with the NSAID had significantly improved memory, indistinguishable from wild-type littermates until the sixth day of training. Similarly, 3× Tg mice were impaired during a short-term and long-term memory probe trial, while the NSAID-treated animals did not differ significantly from wild-type controls. No differences in swimming speed were found. Five months of COX inhibition also reduced intraneuronal Aβ levels and reduced the number of hyperphosphorylated tau-immunoreactive neurons in the hippocampus. Unfortunately, no attempt to correlate levels of Aβ or tau with learning or memory performance was made. Nevertheless, this study shows that chronic treatment with a nonselective COX inhibitor is able to prevent spatial memory deficits and reduce Aβ and hyperphosphorylated tau levels in the 3× Tg model of AD.

Taken together, these collective behavioral studies demonstrate that NSAIDs are quite efficacious in preventing neuroinflammation-induced memory deficits in rodents following LPS, TBI, aging, and models of AD. Both acute and chronic treatments have been shown beneficial, although the age of onset and duration of dosing are critical to the drug's success. Whether the memory-improving effects of NSAIDs are due to the reduction of physiologically elevated PGs or other anti-inflammatory or Aβ-lowering abilities is still largely unclear, although the studies reviewed here suggest at least some of the beneficial effects are independent of alterations in amyloid deposition. More studies quantifying levels of a range of pro-inflammatory molecules including PGE_2 after NSAID treatment are needed, and these should be correlated with learning performance.

Pharmacological Elevations in Prostaglandins

The previous section reviewed a number of studies demonstrating that NSAIDs are frequently successful in preventing memory deficits following diverse neuroinflammatory states. To study more directly the relationship between elevated PGs and memory, experimenters have pharmacologically increased PG levels and tested learning ability. Specifically, we will review studies that elevated PGs by (1) direct injection of IL-1β, a potent COX stimulator, (2) COX-2 overexpression, and (3) direct intra-hippocampal PGE_2 injection.

IL-1β Injection

IL-1β is a potent COX-2 stimulator and has been shown to increase PGE_2 production [13]. A number of researchers have now shown that when injected into the brain, IL-1β impairs hippocampal-dependent memory. Barrientos et al. [23, 93] demonstrated that intra-hippocampal IL-1β injection (1 or 10 ng, respectively) impaired contextual but not auditory fear conditioning, indicating a disruption in hippocampal-specific memory formation. In these studies, IL-1β itself or a multitude of other neuroinflammatory molecules could disrupt the memory formation processes. However, using the same method and dose, Hein et al. [26] found that a nonselective COX inhibitor (naproxen 1 μg/

side) co-administered with IL-1β (10 ng/side) intrahippocampally prevented this contextual memory deficit. Moreover, they showed that IL-1β injection significantly increased hippocampal COX-2 mRNA expression, which was attenuated in rats also receiving nonselective COX inhibition.

Matsumoto et al. [94] also showed that intrahippocampal IL-1β injection (100 ng/side 10 min before testing) significantly impaired working memory in the three-panel runway task. Administration of a COX-2 preferential inhibitor (diclofenac, 10 mg/kg but not 3.2 mg/kg s.c.) 30 min before the IL-1β injection prevented this deficit. In a separate experiment, they showed that PGE_2 was significantly elevated 10 min after intrahippocampal IL-1β injection (100 ng/side). Taken together, these studies show that direct injection of IL-1β into the brain, which reduces confounding peripheral effects, increases COX-2 mRNA and PGE_2 within the hippocampus and impairs hippocampal-dependent long-term and working memory. Moreover, nonselective and COX-2 preferential inhibition prevents these memory deficits. Therefore, the memory impairing effect of acute IL-1β injection appears to be PG-dependent.

COX-2 Overexpression

Instead of inducing COX-2 mRNA and PGE_2 expression by IL-1β injection, Tg mice can be utilized that overexpress human COX-2. Andreasson et al. [95] developed such mice and found that hCOX-2 overexpression drives a ten- to 15-fold elevation in brain PGE_2 levels, which is preventable with administration of a COX-2 inhibitor. In the MWM, 12- and 20-month-old, but not 7-month-old, COX-2-Tg mice were impaired in their memory for the hidden platform, while no differences were found in swim speed or distance to reach a visible platform. In active and inhibitory avoidance tasks, 20-month-old, but not 7- or 12-month-old, Tg animals were significantly impaired, while no significant differences in sensitivity to shock were found between genotypes. These data indicate that hCOX-2 overexpression and the resultant brain PGE_2 increases lead to strong age-dependent hippocampal memory deficits. It is interesting, and perhaps surprising, that 7-month-old Tg mice are not impaired in these tasks as well. However, since the COX-2 transgene is expressed from birth, compensatory processes may work to counter the elevated PGE_2 levels. As the animal continues to age, these processes may fail to sufficiently counter the neuroinflammation, and memory deficits result. Andreasson et al. [95] offers some evidence supporting this idea by showing elevated brain glial fibrillary acid protein levels in 20- to 24-month-old Tg compared to wild-type mice indicating astrocyte activation. Transgenic mice also had increased numbers of apoptotic cells compared to wild-type mice at 14 and 22 months and compared to 8-month-old Tg mice.

PGE_2 Injection

The most direct way to assess whether or not elevated PGs impair hippocampal-dependent memory is to inject PGs into the hippocampus and test learning and memory. Two studies have done just that. Matsumoto et al. [94] intrahippocampally injected PGE_2 (0.01, 0.1, and 1 μg/side) 10 min before testing working memory in the three-panel runway task. Rats injected with either the middle or high dose of PGE_2 had significantly more errors than vehicle-injected rats. Hein et al. [26] also examined the direct effect of PGE_2 on hippocampal-dependent long-term memory. Given the short half-life of PGE_2 in vivo (minutes) and the long period over which memory consolidation occurs (hours), PGE_2 (250 or 500 ng/h for 6 h) or vehicle was continuously infused into the hippocampus of rats immediately after contextual fear conditioning. Rats infused with PGE_2 but not vehicle showed significant impairments in long-term contextual fear memory. These studies provide the most direct evidence that pharmacologically elevated PGE_2 is sufficient to impair hippocampal-dependent memory processes.

Mechanism for Memory-Impairing Effect of PGs

LTP Studies

LTP is a useful model for studying molecular mechanisms involved in synaptic plasticity, and recent studies indicate LTP may occur during memory formation [96]. Many researchers have examined the detrimental effects of neuroinflammation on LTP in the hippocampal formation. LPS, TBI, aging, Aβ application, and IL-1β application have all been shown to impair hippocampal LTP [72, 86, 97–100]. However, whether one underlying mechanism or many diverse pathways are involved in these neuroinflammation-induced LTP deficits is unknown. Given the success of NSAIDs in reversing behavioral memory impairments following these neuroinflammatory conditions, one might expect elevated PGE_2 to be a main suspect and NSAIDs to reverse the LTP impairments as well. Surprisingly, few researchers have published studies examining the ability of NSAIDs to reverse these LTP deficits. Most researchers using NSAIDS in LTP studies investigate the important role of basal levels of PGs in LTP.

Kotilinek et al. [86] found COX-2 inhibition sufficient to restore LTP after Aβ application to hippocampal slices. In vitro application of soluble, synthetic $A\beta_{42}$ to rat hippocampal slices prevented the induction of LTP at the

perforant pathway. Pretreatment with a nonselective (ibuprofen and naproxen) or COX-2 selective (MF tricyclic and NS-398) but not a COX-1 selective (piroxicam) inhibitor prevented inhibition of LTP by $A\beta_{42}$. Moreover, this LTP-restoring effect was abolished by application of exogenous PGE_2, suggesting that COX-2-mediated elevations in PGs are responsible for $A\beta_{42}$-induced LTP deficits. Despite this example of NSAIDs successfully preventing LTP deficits, Shaw et al. [72] found no restoration of LTP by COX inhibition following LPS treatment. Rats were injected with a nonselective COX inhibitor (ibuprofen, 30 mg/kg, i.p.) 1 h before LPS (250 μg/kg i.p.) and recordings done in the perforant pathway 4 h later. Although this drug treatment regimen was able to reverse behavioral deficits in the MWM, no beneficial effect on the induction of LTP was found. Large differences between these studies exist, both in the treatment that impairs LTP ($A\beta_{42}$ vs. LPS) and in the methodology (in vitro vs. in vivo manipulations). Whether the lack of studies using NSAIDs to prevent inflammation-induced LTP deficits is indicative of a truly unexamined research area or a plethora of unpublished negative results is unknown. Regardless, more studies examining the effect of COX inhibition on LTP deficits following neuroinflammatory conditions are needed.

EP3R Hypothesis

Although the LTP literature does not reveal potential mechanisms to explain how elevated PGs might impair synaptic plasticity during neuroinflammatory states, we propose one hypothesis. As discussed above, PGE_2 signals through four EP receptors, EP1–4. Interestingly, the EP3R has the highest abundance within the hippocampus and colabels with PSD95 indicating neuronal expression at the postsynaptic density [68]. In an LTP model, this would place the EP3R in an ideal location to interfere with postsynaptic molecular cascades needed for synaptic strengthening and, potentially, memory. Moreover, the EP3R can be upregulated by neuroinflammatory conditions. In vitro, hypothalamic neurons treated with glial-conditioned media upregulate EP3R mRNA, but not EPR 1, 2, or 4 mRNA [101]. In addition, human astrocytoma cells, primary human astrocytes, and rat mixed glial cultures incubated with IL-1β for 24 h showed EP3R mRNA and protein expression [102]. In vivo, IL-1β injection (20 μg) into the lateral ventricle increased EP3R protein 24 h later within the hippocampus [102]. Vehicle-injected animals also had highly elevated EP3R protein (20-fold above non-injected controls), likely resulting from significant neuroinflammation arising from the injection stab wound [102]. IL-1β injection caused a further twofold elevation in EP3R protein above vehicle-injected levels [102]. Although it bears mentioning that there is a higher than expected mobility for the EP3R protein seen on Western blot in the aforementioned study, IL-1β which is elevated during neuroinflammation appears to upregulate EP3Rs in vitro and in vivo.

In order to understand how PGE_2 could act through the EP3R to interfere with postsynaptic signaling requisite for synaptic strengthening, we must first introduce a key player in synaptic strengthening and memory formation. Elevations in one immediate early gene, brain-derived neurotrophic factor (BDNF), following a learning event have been shown essential for long-term hippocampal-dependent memory [103]. Conditions that physiologically reduce BDNF or injection of BDNF antisense oligonucleotides impair memory, and manipulations that elevate BDNF improve memory [104–107]. Moreover, animals with genetically reduced BDNF show hippocampal LTP and memory deficits, and application of BDNF can restore normal LTP and memory [108–111].

BDNF mRNA is increased postsynaptically in hippocampal slices following LTP-inducing high-frequency stimulation (HFS). This HFS initiates molecular intracellular cascades resulting in the activation of NMDA receptors, increased Ca^{2+} influx, and elevated cAMP. Cyclic AMP is a second messenger that can activate a number of kinase pathways including the PKA and Ras/MAPK pathways. These kinases can translocate into the nucleus and phosphorylate the cAMP response element-binding protein (CREB). Once phosphorylated, CREB acts as a transcription factor, binding to the cAMP response element (CRE) and upregulating transcription of downstream genes (see Fig. 2). BDNF is one gene whose transcription is regulated by CREB.

Activation of the EP3R by PGE_2 predominantly reduces cAMP through an inhibitory G protein. Therefore, one result of elevated hippocampal PGE_2 may be to reduce activity-dependent BDNF transcription necessary for long-term memory formation through either of the aforementioned kinase pathways. Rage et al. [101] first proposed this hypothesis, and two studies support the idea. Rage et al. [101] showed that IL-1β application to mixed hypothalamic neuron and glial cultures reduced BDNF mRNA and protein, and a nonselective COX inhibitor (indomethacin) prevented this reduction in BDNF. Direct application of PGE_2 to the cultures also reduced BDNF mRNA and protein. Moreover, astrocyte-conditioned media applied to neuron-enriched cultures increased EP3R mRNA but not EP1 or EP4. Interestingly, IL-1β or PGE_2 applied to neuron-enriched cultures lacking glial cells actually increased BDNF mRNA and protein, suggesting that the glial- or inflammation-induced increase in EP3R is necessary for the BDNF-lowering effect of these molecules. Extending this work to an in vivo system, Hein et al. [26] demonstrated that direct infusion of PGE_2 into the

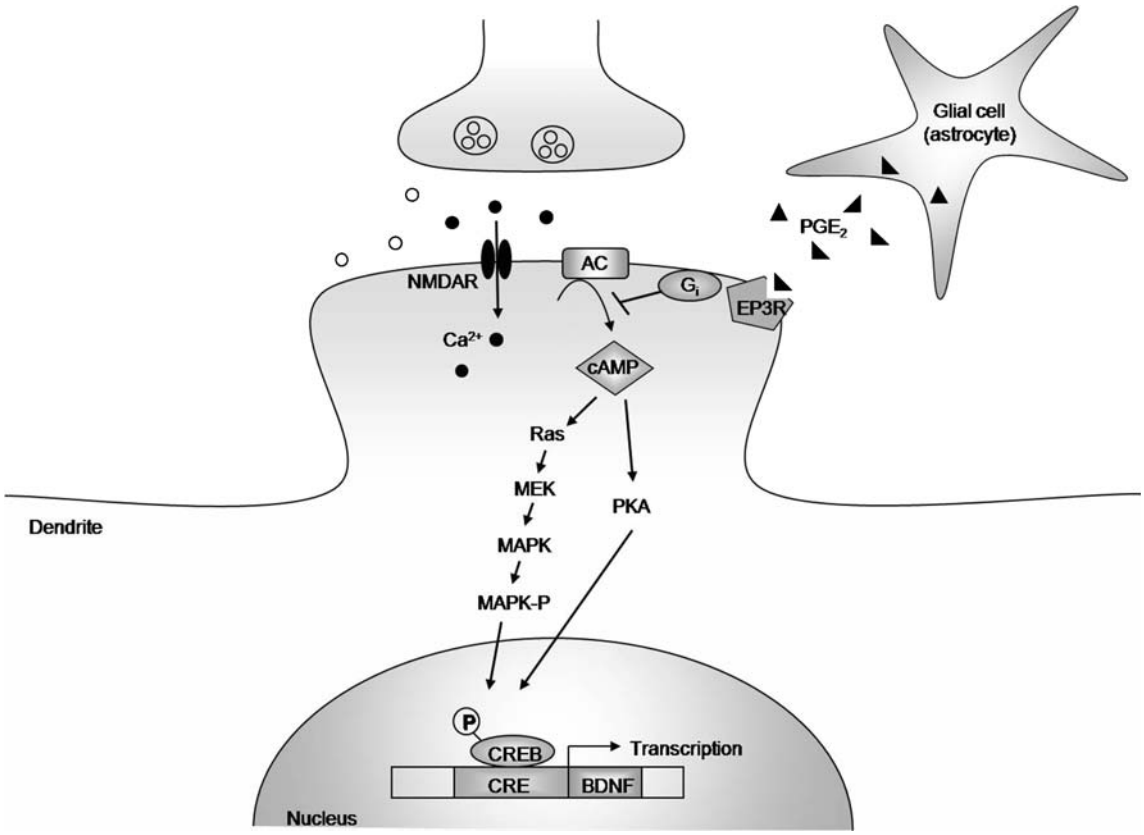

Fig. 2 EP3R-BDNF hypothesis for LTP and memory impairing effect of elevated PGE_2. Normally, HFS causes the release of glutamate, activation of NMDARs, and increase in intracellular calcium. Adenylyl cyclase (AC) is then activated to produce cAMP and activate the Ras/MAPK or PKA pathways. These kinases translocate to the nucleus and phosphorylate CREB. Phosphorylated CREB (pCREB) increases transcription of downstream genes including BDNF, which is necessary for LTP and memory formation. When PGE_2 is elevated under neuroinflammatory conditions, it binds to postsynaptic EP3Rs and predominately activates G_i proteins to inhibit the production of cAMP. This activity would dampen the signal to increase BDNF expression and could account for impairments in LTP and memory formation following inflammation. 3'-5'-cyclic adenosine monophosphate (cAMP), mitogen-activated protein (MAP) kinase, MAPK kinase (MEK), *N*-methyl-D-aspartic acid (NMDA), protein kinase A (PKA)

hippocampus after contextual fear conditioning impairs long-term memory for the context and reduces the hippocampal BDNF mRNA induction seen 2 h after conditioning. Therefore, some neuroinflammation-induced memory deficits may be caused by elevated PGE_2 binding to increased numbers of EP3Rs, reducing cAMP levels, and thereby reducing the necessary BDNF mRNA induction. Further studies are needed to test this hypothesis.

Methodological Considerations: COX-Independent Actions of NSAIDs

The above mechanistic hypothesis may explain memory deficits in some neuroinflammatory conditions but not others. For example, it is easy to imagine how EP3R activation could disrupt synaptic strengthening mechanisms following an acute inflammatory challenge, e.g., injection of IL-1β, PGE_2, LPS, etc. However, under more chronic neuroinflammatory states, such as aging or AD models, many complex and potentially compensatory changes have likely occurred within the brain. In these conditions, chronic dosing of NSAIDs for weeks and often months is used to prevent memory impairments. If a simple reduction in cAMP and BDNF from EP3R activation was responsible, one would expect acute dosing of NSAIDs to be sufficient to improve memory. Thus, with chronic dosing, COX-independent actions of NSAIDs such as reducing reactive oxygen species (ROS) levels, inhibiting NF-kB, activating PPARγ, and/or reducing Aβ may explain some of the beneficial effects of NSAIDs. These possibilities are described in more detail below.

As a by-product of the oxidation step of the COX reaction, ROS are generated. Therefore, inhibition of COX inherently reduces the production of ROS. ROS can initiate a host of harmful events within the cell, most notably oxidative damage to lipids and proteins. Although the cell can effectively scavenge ROS under basal conditions, with increased inflammatory burden, the cell's scavenging mechanisms are insufficient, and severe oxidative damage

can occur. In aged animals, ROS levels are negatively correlated with memory performance [112]. Moreover, reducing levels of ROS with antioxidant-enriched diets, superoxide dismutase/catalase mimetics, or Tg superoxide dismutase overexpression improves LTP and hippocampal-dependent memory in aged animals [113–120]. These data indicate that in animals with an elevated ROS burden, simply reducing ROS is sufficient to improve memory function (see [121] for review).

In addition to their inherent reduction of ROS, some NSAIDs have other biological activities besides inhibiting COX that may impact learning and memory processes directly or indirectly. Ibuprofen has been shown to inhibit NF-κB, a powerful pro-inflammatory transcription factor that upregulates a milieu of cytokines, and IKK, a related pro-inflammatory kinase [122, 123]. Ibuprofen and indomethacin can activate PPARγ, an anti-inflammatory nuclear receptor that reduces the transcription of pro-inflammatory cytokines such as IL-1β [124, 125]. Ibuprofen, indomethacin, and sulindac reduce levels of $A\beta_{42}$ by as much as 80% ([126]; see [127] for review). Interestingly, researchers have shown that many of these actions individually are sufficient to improve memory function. PPARγ agonists improved object recognition memory in rats following whole brain irradiation and enhanced spatial memory performance in the MWM in rats fed high-fat diets [128, 129]. In addition, *R*-flurbiprofen, which can reduce Aβ levels and inhibit NF-κB without reducing COX activity at therapeutic doses, improved spatial memory in the MWM in animal models of AD [130]. The exact profile of which NSAIDs have these COX-independent actions and what doses are necessary is not fully known. However, studies should take into account the known side effects when selecting drugs and doses as well as deciding what molecular markers within the brain to measure. When additional molecular markers such as IL-1, corticosterone, or Aβ, are measured, the levels of these markers should be correlated with behavioral performance. Such analyses may help identify the critical actions of NSAIDs in therapeutic studies.

NSAIDs in Alzheimer's Disease

Much of the initial interest in using NSAIDs to treat AD arose from epidemiological studies showing that long-term NSAID use in normal aging populations reduced the risk of developing AD. Incidence, case control, and population-based prevalence studies have all repeatedly found significant or near significant reductions in the incidence of AD in aging populations with long-term and usually nonselective COX inhibitor use. These studies have been reviewed extensively by McGeer and McGeer [131]. Unfortunately, recent clinical trials have been unable to find such benefits of NSAIDs when patients already diagnosed with AD were treated. A couple of initial studies with nonselective COX inhibitors found significant or beneficial trends in improved cognitive outcome [132, 133]. However, numerous large-scale clinical trials with COX-2 selective inhibitors and even a few with nonselective COX inhibitors have found no beneficial effect and even potential further cognitive impairment or increased cardiovascular risk when given to patients with mild to moderate AD [134–140]. The lack of NSAID efficacy in symptomatic AD patients may be due to one or more factors, including a profound loss of hippocampal/cortical neurons, inability to rewire, or the inhibition of beneficial PG signaling pathways. Therefore, despite the overwhelming ability of NSAIDs to prevent or reverse cognitive deficits following neuroinflammatory states in animals, they do not appear sufficient to slow the progression or improve cognitive function in symptomatic AD patients.

Why animal models of AD benefit from NSAID treatment but AD patients do not is unknown. However, one difference between these conditions is striking: the degree of neuronal loss before onset of treatment. By the time the first clinical symptoms of AD appear, the human hippocampal circuitry has already suffered extensive neuronal loss. Even in very mild AD, researchers have reported 50% neuron loss in layer II of the entorhinal cortex and 46% loss in CA1 of the hippocampus [141]. Therefore, until a biomarker for AD can be found to diagnose AD before clinical symptoms appear, doctors must treat patients' whose neural substrate for memory is already compromised. The same is not true in the animal models of AD. Few, if any, of the animal models of AD show neuronal loss and certainly not to the extent seen in the human AD condition [142]. This difference may explain the seemingly contradictory data generated from NSAID treatment. In animal models of AD, NSAIDs reduce the neuroinflammation and potentially Aβ levels (see comments above) and are therefore able to restore normal cognitive function. However, in human AD, the neurological substrate for forming new memories, the hippocampal circuitry, is greatly disrupted, and reducing inflammation or Aβ is not sufficient to restore cognitive abilities.

Conclusions

This paper reviews a significant body of literature showing that PGs are elevated under inflammatory conditions within the hippocampus, a brain structure critical for learning and memory. Within the hippocampus, the EP3R for PGE_2 is increased at postsynaptic sites with neuroinflammation. Moreover, NSAIDs have a powerful ability to improve

memory in rodent models of neuroinflammation, and COX-2 overexpression or intra-hippocampal PGE_2 injection can impair memory (see Table 1). Finally, PGE_2 signaling, likely through the EP3R, can reduce BDNF, a molecule necessary for normal hippocampal-dependent memory. Taken together, this evidence indicates that PGs are responsible for at least some types of neuroinflammation-induced memory deficits.

References

1. Draper K, Ponsford J (2008) Cognitive functioning ten years following traumatic brain injury and rehabilitation. Neuropsychology 22(5):618–625
2. Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz LM, Koschera A (2004) Progression of cognitive impairment in stroke patients. Neurology 63(9):1618–1623
3. Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, White CL 3rd, Araoz C (1989) Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A 86(19):7611–7615
4. Griffin DE, Wesselingh SL, McArthur JC (1994) Elevated central nervous system prostaglandins in human immunodeficiency virus-associated dementia. Ann Neurol 35(5):592–597
5. Perrella O, Carrieri PB, Guarnaccia D, Soscia M (1992) Cerebrospinal fluid cytokines in AIDS dementia complex. J Neurol 239(7): 387–388
6. Dantzer R, Kelley KW (2007) Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 21 (2):153–160
7. Katsuura G, Arimura A, Koves K, Gottschall P (1990) Involvement of organum vasculosum of lamina terminalis and preoptic area in interleukin 1 beta-induced ACTH release. Am J Physiol 258(1):163–171
8. Banks W, Ortiz L, Plotkin S, Kastin A (1991) Human interleukin (IL) 1 alpha, murine IL-1 alpha and murine IL-1 beta are transported from blood to brain in the mouse by a shared saturable mechanism. J Pharmacol Exp Ther 259(3):988–996
9. Watkins L, Goehler L, Relton J, Tartaglia N, Silbert L, Martin D, Maier S (1995) Blockade of interleukin-1 induced hyperthermia by subdiaphragmatic vagotomy: evidence for vagal mediation of immune-brain communication. Neurosci Lett 183(1–2):27–31
10. Fleshner M, Goehler L, Schwartz B, McGorry M, Martin D, Maier S, Watkins L (1998) Thermogenic and corticosterone responses to intravenous cytokines (IL-1beta and TNF-alpha) are attenuated by subdiaphragmatic vagotomy. J Neuroimmunol 86 (2):134–141
11. Watkins L, Maier S, Goehler L (1995) Cytokine-to-brain communication: a review and analysis of alternative mechanisms. Life Sci 57(11):1011–1026
12. Shaftel SS, Kyrkanides S, Olschowka JA, Miller JN, Johnson RE, O'Banion MK (2007) Sustained hippocampal IL-1 beta overexpression mediates chronic neuroinflammation and ameliorates Alzheimer plaque pathology. J Clin Invest 117(6):1595–1604
13. O'Banion MK, Miller JC, Chang JW, Kaplan MD, Coleman PD (1996) Interleukin-1 beta induces prostaglandin G/H synthase-2 (cyclooxygenase-2) in primary murine astrocyte cultures. J Neurochem 66(6):2532–2540
14. Ristimaki A, Garfinkel S, Wessendorf J, Maciag T, Hla T (1994) Induction of cyclooxygenase-2 by interleukin-1 alpha. Evidence for post-transcriptional regulation. J Biol Chem 269(16): 11769–11775
15. Shaftel SS, Carlson TJ, Olschowka JA, Kyrkanides S, Matousek SB, O'Banion MK (2007) Chronic interleukin-1beta expression in mouse brain leads to leukocyte infiltration and neutrophil-independent blood brain barrier permeability without overt neurodegeneration. J Neurosci 27(35):9301–9309
16. Avitsur R, Pollak Y, Yirmiya R (1997) Administration of interleukin-1 into the hypothalamic paraventricular nucleus induces febrile and behavioral effects. Neuroimmunomodulation 4(5–6):258–265
17. Bretdibat J, Bluthe R, Kent S, Kelley K, Dantzer R (1995) Lipopolysaccharide and interleukin-1 depress food-motivated behavior in mice by a vagal-mediated mechanism. Brain Behav Immun 9(3):242–246
18. Kent S, Bluthe R, Dantzer R, Hardwick A, Kelley K, Rothwell N, Vannice J (1992) Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1. Proceedings of the National Academy of Sciences 89(19):9117–9120
19. Oitzl M, Van Oers H, Schobitz B, Ron de Kloet E (1993) Interleukin-1 ß, but not interleukin-6, impairs spatial navigation learning. Brain Res 613(1):160–163
20. Gibertini M, Newton C, Friedman H, Klein T (1995) Spatial learning impairment in mice infected with *Legionella pneumophila* or administered exogenous interleukin-1-ß. Brain Behav Immun 9(2):113–128
21. Casadesus G, Smith MA, Basu S, Hua J, Capobianco DE, Siedlak SL, Zhu X, Perry G (2007) Increased isoprostane and prostaglandin are prominent in neurons in Alzheimer disease. Mol Neurodegener 2:2
22. Montine TJ, Sidell KR, Crews BC, Markesbery WR, Marnett LJ, Roberts LJ 2nd, Morrow JD (1999) Elevated CSF prostaglandin E2 levels in patients with probable AD. Neurology 53(7): 1495–1498
23. Barrientos RM, Higgins EA, Sprunger DB, Watkins LR, Rudy JW, Maier SF (2002) Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behav Brain Res 134(1–2):291–298
24. Pugh CR, Nguyen KT, Gonyea JL, Fleshner M, Wakins LR, Maier SF, Rudy JW (1999) Role of interleukin-1 beta in impairment of contextual fear conditioning caused by social isolation. Behav Brain Res 106(1–2):109–118
25. Pugh CR, Kumagawa K, Fleshner M, Watkins LR, Maier SF, Rudy JW (1998) Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. Brain Behav Immun 12(3):212–229
26. Hein AM, Stutzman DL, Bland ST, Barrientos RM, Watkins LR, Rudy JW, Maier SF (2007) Prostaglandins are necessary and sufficient to induce contextual fear learning impairments after interleukin-1 beta injections into the dorsal hippocampus. Neuroscience 150(4):754–763
27. Song C, Horrobin D (2004) Omega-3 fatty acid ethyl-eicosapentaenoate, but not soybean oil, attenuates memory impairment induced by central IL-1beta administration. J Lipid Res 45(6):1112–1121
28. Pugh CR, Johnson JD, Martin D, Rudy JW, Maier SF, Watkins LR (2000) Human immunodeficiency virus-1 coat protein gp120 impairs contextual fear conditioning: a potential role in AIDS related learning and memory impairments. Brain Res 861(1):8–15
29. Hein AM, Stasko, MR, Matousek SB, Walter JR, Scott-McKean JJ, Watkins LR, SF, Costa ACS, O'Banion MK (2008) Chronic hippocampal IL-1β overexpression impairs contextual but not auditory fear memory, in Proc Soc Neurosci. Washington D.C.
30. Pugh RC, Fleshner M, Watkins LR, Maier SF, Rudy JW (2001) The immune system and memory consolidation: a role for the cytokine IL-1beta. Neurosci Biobehav Rev 25(1):29–41

31. Mark KS, Trickler WJ, Miller DW (2001) Tumor necrosis factor-alpha induces cyclooxygenase-2 expression and prostaglandin release in brain microvessel endothelial cells. J Pharmacol Exp Ther 297(3):1051–1058
32. Salvemini D, Misko TP, Masferrer JL, Seibert K, Currie MG, Needleman P (1993) Nitric oxide activates cyclooxygenase enzymes. Proc Natl Acad Sci U S A 90(15):7240–7244
33. Kuraishi Y, Ushikubi F (2001) Pain, fever and prostanoids. Nippon Yakurigaku Zasshi 117(4):248–254
34. Dinarello CA, Gatti S, Bartfai T (1999) Fever: links with an ancient receptor. Curr Biol 9(4):R147–R150
35. Swiergiel AH, Dunn AJ (2002) Distinct roles for cyclooxygenases 1 and 2 in interleukin-1-induced behavioral changes. J Pharmacol Exp Ther 302(3):1031–1036
36. Pecchi E, Dallaporta M, Thirion S, Salvat C, Berenbaum F, Jean A, Troadec JD (2006) Involvement of central microsomal prostaglandin E synthase-1 in IL-1beta-induced anorexia. Physiol Genomics 25(3):485–492
37. De La Garza R II, Asnis GM, Fabrizio KR, Pedrosa E (2005) Acute diclofenac treatment attenuates lipopolysaccharide-induced alterations to basic reward behavior and HPA axis activation in rats. Psychopharmacology 179(2):356–365
38. Crestani F, Seguy F, Dantzer R (1991) Behavioural effects of peripherally injected interleukin-1: role of prostaglandins. Brain Res 542(2):330–335
39. Morris R (1984) Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11(1):47–60
40. Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106(2):274–285
41. Hodges H (1996) Maze procedures: the radial-arm and water maze compared. Brain Res Cogn Brain Res 3(3–4):167–181
42. Gerlai R (2001) Behavioral tests of hippocampal function: simple paradigms complex problems. Behav Brain Res 125(1–2): 269–277
43. McDonald R, Hong N, Devan B (2004) The challenges of understanding mammalian cognition and memory-based behaviours: an interactive learning and memory systems approach. Neurosci Biobehav Rev 28(7):719–745
44. Chen C, Magee JC, Bazan NG (2002) Cyclooxygenase-2 regulates prostaglandin E2 signaling in hippocampal long-term synaptic plasticity. J Neurophysiol 87(6):2851–2857
45. Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, Levy-Lahad E, Yirmiya R (2007) A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 32(8–10):1106–1115
46. Cowley TR, Fahey B, O'Mara SM (2008) COX-2, but not COX-1, activity is necessary for the induction of perforant path long-term potentiation and spatial learning in vivo. Eur J NeuroSci 27 (11):2999–3008
47. Teather LA, Packard MG, Bazan NG (2002) Post-training cyclooxygenase-2 (COX-2) inhibition impairs memory consolidation. Learn Memory 9(1):41–47
48. Rall JM, Mach SA, Dash PK (2003) Intrahippocampal infusion of a cyclooxygenase-2 inhibitor attenuates memory acquisition in rats. Brain Res 968(2):273–276
49. Sharifzadeh M, Naghdi N, Khosrovani S, Ostad SN, Sharifzadeh K, Roghani A (2005) Post-training intrahippocampal infusion of the COX-2 inhibitor celecoxib impaired spatial memory retention in rats. Eur J Pharmacol 511(2–3):159–166
50. Shaw KN, Commins S, O'Mara SM (2003) Deficits in spatial learning and synaptic plasticity induced by the rapid and competitive broad-spectrum cyclooxygenase inhibitor ibuprofen are reversed by increasing endogenous brain-derived neurotrophic factor. Eur J NeuroSci 17(11):2438–2446
51. Larson SJ, Hartle KD, Ivanco TL (2007) Acute administration of interleukin-1beta disrupts motor learning. Behav Neurosci 121 (6):1415–1420
52. Fiore M, Angelucci F, Alleva E, Branchi I, Probert L, Aloe L (2000) Learning performances, brain NGF distribution and NPY levels in transgenic mice expressing TNF-alpha. Behav Brain Res 112(1–2):165–175
53. Heyser C, Masliah E, Samimi A, Campbell I, Gold L (1997) Progressive decline in avoidance learning paralleled by inflammatory neurodegeneration in transgenic mice expressing interleukin 6 in the brain. National Acad Sciences. p. 1500–1505.
54. Bjugstad K, Flitter W, Garland W, Su G, Arendash G (1998) Preventive actions of a synthetic antioxidant in a novel animal model of AIDS dementia. Brain Res 795(1–2):349–357
55. Song C, Leonard BE, Horrobin DF (2004) Dietary ethyl-eicosapentaenoic acid but not soybean oil reverses central interleukin-1-induced changes in behavior, corticosterone and immune response in rats. Stress 7(1):43–54
56. Lupien S, de Leon M, de Santi S, Convit A, Tarshish C, Nair N, Thakur M, McEwen B, Hauger R, Meaney M (1998) Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1(1):69–73
57. O'Banion MK (1999) Cyclooxygenase-2: molecular biology, pharmacology, and neurobiology. Crit Rev Neurobiol 13(1):45–82
58. Tanabe T, Tohnai N (2002) Cyclooxygenase isozymes and their gene structures and expression. Prostaglandins Other Lipid Mediat 68–69:95–114
59 Bliss, SP, Shaftel SS, Olschowka JA, Kyrkanides S, O'Banion MK (2007) Chronic hippocampal IL-1β expression elevates PGE2 production in a cyclooxygenase I dependent manner, in Proc Soc Neurosci. San Diego, CA.
60. Shaftel SS, Olschowka JA, Hurley SD, Moore AH, O'Banion MK (2003) COX-3: a splice variant of cyclooxygenase-1 in mouse neural tissue and cells. Brain Res Mol Brain Res 119(2):213–215
61. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL (2002) COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci U S A 99(21):13926–13931
62. Kis B, Snipes JA, Gaspar T, Lenzser G, Tulbert CD, Busija DW (2006) Cloning of cyclooxygenase-1b (putative COX-3) in mouse. Inflammation Res 55(7):274–278
63. Quan N, Whiteside M, Herkenham M (1998) Cyclooxygenase 2 mRNA expression in rat brain after peripheral injection of lipopolysaccharide. Brain Res 802(1–2):189–197
64. Gopez JJ, Yue H, Vasudevan R, Malik AS, Fogelsanger LN, Lewis S, Panikashvili D, Shohami E, Jansen SA, Narayan RK, Strauss KI (2005) Cyclooxygenase-2-specific inhibitor improves functional outcomes, provides neuroprotection, and reduces inflammation in a rat model of traumatic brain injury. Neurosurgery 56(3):590–604
65. Casolini P, Catalani A, Zuena AR, Angelucci L (2002) Inhibition of COX-2 reduces the age-dependent increase of hippocampal inflammatory markers, corticosterone secretion, and behavioral impairments in the rat. J Neurosci Res 68(3):337–343
66. Narumiya S, Sugimoto Y, Ushikubi F (1999) Prostanoid receptors: structures, properties, and functions. Physiol Rev 79 (4):1193–1226
67. Sugimoto Y, Namba T, Honda A, Hayashi Y, Negishi M, Ichikawa A, Narumiya S (1992) Cloning and expression of a cDNA for mouse prostaglandin E receptor EP3 subtype. J Biol Chem 267(10):6463–6466
68. Zhu P, Genc A, Zhang X, Zhang J, Bazan NG, Chen C (2005) Heterogeneous expression and regulation of hippocampal prostaglandin E2 receptors. J Neurosci Res 81(6):817–826

69. Weidenfeld J, Crumeyrolle-Arias M, Haour F (1995) Effect of bacterial endotoxin and interleukin-1 on prostaglandin biosynthesis by the hippocampus of mouse brain: role of interleukin-1 receptors and glucocorticoids. Neuroendocrinology 62(1):39–46
70. Deak T, Bellamy C, Bordner KA (2005) Protracted increases in core body temperature and interleukin-1 following acute administration of lipopolysaccharide: implications for the stress response. Physiol Behav 85(3):296–307
71. Jain NK, Patil CS, Kulkarni SK, Singh A (2002) Modulatory role of cyclooxygenase inhibitors in aging- and scopolamine or lipopolysaccharide-induced cognitive dysfunction in mice. Behav Brain Res 133(2):369–376
72. Shaw KN, Commins S, O'Mara SM (2005) Cyclooxygenase inhibition attenuates endotoxin-induced spatial learning deficits, but not an endotoxin-induced blockade of long-term potentiation. Brain Res 1038(2):231–237
73. Ma TC, Zhu XZ (1997) Suppression of lipopolysaccharide-induced impairment of active avoidance and interleukin-6-induced increase of prostaglandin E2 release in rats by indometacin. Arzneimittelforschung 47(5):595–597
74. Hauss-Wegrzyniak B, Vraniak P, Wenk G (1999) The effects of a novel NSAID on chronic neuroinflammation are age dependent. Neurobiol Aging 20(3):305–313
75. Jin D, Sung J, Hwang Y, Kwon K, Han S, Min S, Han J (2008) Dexibuprofen (*S* (+)-isomer ibuprofen) reduces microglial activation and impairments of spatial working memory induced by chronic lipopolysaccharide infusion. Pharmacol Biochem Behav 89(3):404–411
76. Cernak I, O'Connor C, Vink R (2002) Inhibition of cyclooxygenase 2 by nimesulide improves cognitive outcome more than motor outcome following diffuse traumatic brain injury in rats. Exp Brain Res 147(2):193–199
77. Dash P, Mach S, Moore A (2000) Regional expression and role of cyclooxygenase-2 following experimental traumatic brain injury. J Neurotrauma 17(1):69–81
78. Frank MG, Barrientos RM, Biedenkapp JC, Rudy JW, Watkins LR, Maier SF (2006) mRNA up-regulation of MHC II and pivotal pro-inflammatory genes in normal brain aging. Neurobiol Aging 27(5):717–722
79. Mesches MH, Gemma C, Veng LM, Allgeier C, Young DA, Browning MD, Bickford PC (2004) Sulindac improves memory and increases NMDA receptor subunits in aged Fischer 344 rats. Neurobiol Aging 25(3):315–324
80. Bishnoi M, Patil CS, Kumar A, Kulkarni SK (2005) Protective effects of nimesulide (COX Inhibitor), AKBA (5-LOX Inhibitor), and their combination in aging-associated abnormalities in mice. Methods Find Exp Clin Pharmacol 27(7):465–470
81. Joo Y, Kim H, Woo R, Park C, Shin K, Lee J, Chang K, Kim S, Suh Y (2006) Mefenamic acid shows neuroprotective effects and improves cognitive impairment in in vitro and in vivo Alzheimer's disease models. Mol Pharmacol 69(1):76–84
82. Cakala M, Malik A, Strosznajder J (2007) Inhibitor of cyclooxygenase-2 protects against amyloid b peptide-evoked memory impairment in mice. Pharmacol Rep 59(2):164–172
83. Kawarabayashi T, Younkin L, Saido T, Shoji M, Ashe K, Younkin S (2001) Age-dependent changes in brain, CSF, and plasma amyloid beta protein in the Tg2576 transgenic mouse model of Alzheimer's disease. J Neurosci 21(2):372
84. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science 274 (5284):99–102
85. Westerman M, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin L, Carlson G, Younkin S, Ashe K (2002) The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. J Neurosci 22(5):1858
86. Kotilinek L, Westerman M, Wang Q, Panizzon K, Lim G, Simonyi A, Lesne S, Falinska A, Younkin L, Younkin S (2008) Cyclooxygenase-2 inhibition improves amyloid-[beta]-mediated suppression of memory and synaptic plasticity. Brain 131(3):651
87. Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA, Copeland NG, Lee MK, Younkin LH, Wagner SL, Younkin SG, Borchelt DR (2004) Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase. Hum Mol Genet 13(2):159–170
88. Trinchese F, Liu S, Battaglia F, Walter S, Mathews PM, Arancio O (2004) Progressive age-related development of Alzheimer-like pathology in APP/PS1 mice. Ann Neurol 55(6):801–814
89. Melnikova T, Savonenko A, Wang Q, Liang X, Hand T, Wu L, Kaufmann WE, Vehmas A, Andreasson KI (2006) Cycloxygenase-2 activity promotes cognitive deficits but not increased amyloid burden in a model of Alzheimer's disease in a sex-dimorphic pattern. Neuroscience 141(3):1149–1162
90. Oddo S, Caccamo A, Shepherd J, Murphy M, Golde T, Kayed R, Metherate R, Mattson M, Akbari Y, LaFerla F (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles intracellular Aß and synaptic dysfunction. Neuron 39(3):409–421
91. Oddo S, Caccamo A, Kitazawa M, Tseng B, LaFerla F (2003) Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. Neurobiol Aging 24(8):1063–1070
92. McKee A, Carreras I, Hossain L, Ryu H, Klein W, Oddo S, LaFerla F, Jenkins B, Kowall N, Dedeoglu A (2008) Ibuprofen reduces Aß, hyperphosphorylated tau and memory deficits in Alzheimer mice. Brain Res 1207:225–236
93. Barrientos RM, Sprunger DB, Campeau S, Watkins LR, Rudy JW, Maier SF (2004) BDNF mRNA expression in rat hippocampus following contextual learning is blocked by intrahippocampal IL-1beta administration. J Neuroimmunol 155(1–2):119–126
94. Matsumoto Y, Yamaguchi T, Watanabe S, Yamamoto T (2004) Involvement of arachidonic acid cascade in working memory impairment induced by interleukin-1 beta. Neuropharmacology 46(8):1195–1200
95. Andreasson KI, Savonenko A, Vidensky S, Goellner JJ, Zhang Y, Shaffer A, Kaufmann WE, Worley PF, Isakson P, Markowska AL (2001) Age-dependent cognitive deficits and neuronal apoptosis in cyclooxygenase-2 transgenic mice. J Neurosci 21 (20):8198–8209
96. Fedulov V, Rex CS, Simmons DA, Palmer L, Gall CM, Lynch G (2007) Evidence that long-term potentiation occurs within individual hippocampal synapses during learning. J Neurosci 27(30):8031–8039
97. Vereker E, Campbell V, Roche E, McEntee E, Lynch MA (2000) Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. J Biol Chem 275 (34):26252–26258
98. Cunningham AJ, Murray CA, O'Neill LA, Lynch MA, O'Connor JJ (1996) Interleukin-1 beta (IL-1 beta) and tumour necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro. Neurosci Lett 203(1):17–20
99. Miyazaki S, Katayama Y, Lyeth B, Jenkins L, DeWitt D, Goldberg S, Newlon P, Hayes R (1992) Enduring suppression of hippocampal long-term potentiation following traumatic brain injury in rat. Brain Res 585(1–2):335–339
100. Murray C, Lynch M (1998) Dietary supplementation with vitamin E reverses the age-related deficit in long term potentiation in dentate gyrus. J Biol Chem 273(20):12161–12168
101. Rage F, Silhol M, Tapia-Arancibia L (2006) IL-1beta regulation of BDNF expression in rat cultured hypothalamic neurons depends on the presence of glial cells. Neurochem Int 49 (5):433–441

102. Waschbisch A, Fiebich B, Akundi R, Schmitz M, Hoozemans J, Candelario-Jalil E, Virtainen N, Veerhuis R, Slawik H, Yrjanheikki J (2006) Interleukin-1 beta-induced expression of the prostaglandin E2-receptor subtype EP3 in U373 astrocytoma cells depends on protein kinase C and nuclear factor-kappaB. J Neurochem 96 (3):680
103. Alonso M, Vianna MR, Depino AM, Mello e Souza T, Pereira P, Szapiro G, Viola H, Pitossi F, Izquierdo I, Medina JH (2002) BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. Hippocampus 12 (4):551–560
104. Gobbo OL, O'Mara SM (2004) Impact of enriched-environment housing on brain-derived neurotrophic factor and on cognitive performance after a transient global ischemia. Behav Brain Res 152(2):231–241
105. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F (2004) Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. Neuroscience 125(1):129–139
106. Ma YL, Wang HL, Wu HC, Wei CL, Lee EH (1998) Brain-derived neurotrophic factor antisense oligonucleotide impairs memory retention and inhibits long-term potentiation in rats. Neuroscience 82(4):957–967
107. Mu JS, Li WP, Yao ZB, Zhou XF (1999) Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. Brain Res 835(2):259–265
108. Gorski JA, Balogh SA, Wehner JM, Jones KR (2003) Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience 121(2):341–354
109. Heldt SA, Stanek L, Chhatwal JP, Ressler KJ (2007) Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry 12(7):656–670
110. Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER (1996) Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron 16(6):1137–1145
111. Pozzo-Miller L, Gottschalk W, Zhang L, McDermott K, Du J, Gopalakrishnan R, Oho C, Sheng Z, Lu B (1999) Impairments in high-frequency transmission, synaptic vesicle docking, and synaptic protein distribution in the hippocampus of BDNF knockout mice. J Neurosci 19(12):4972–4983
112. Jia JM, Jia JP, Jia L, Shen Y, Pollock M (2003) Relationship between learning ability and memory and free radical in hippocampus of old rats. Zhonghua yi xue za zhi 83(9):796–798
113. Murray CA, Lynch MA (1998) Dietary supplementation with vitamin E reverses the age-related deficit in long term potentiation in dentate gyrus. J Biol Chem 273(20):12161–12168
114. Liu R, Liu IY, Bi X, Thompson RF, Doctrow SR, Malfroy B, Baudry M (2003) Reversal of age-related learning deficits and brain oxidative stress in mice with superoxide dismutase/catalase mimetics. Proc Natl Acad Sci U S A 100(14):8526–8531
115. Levin ED, Christopher NC, Lateef S, Elamir BM, Patel M, Liang LP, Crapo JD (2002) Extracellular superoxide dismutase over-expression protects against aging-induced cognitive impairment in mice. Behav Genet 32(2):119–125
116. Levin ED, Christopher NC, Crapo JD (2005) Memory decline of aging reduced by extracellular superoxide dismutase overexpression. Behav Genet 35(4):447–453
117. Levin ED (2005) Extracellular superoxide dismutase (EC-SOD) quenches free radicals and attenuates age-related cognitive decline: opportunities for novel drug development in aging. Curr Alzheimer Res 2(2):191–196
118. Quick KL, Ali SS, Arch R, Xiong C, Wozniak D, Dugan LL (2008) A carboxyfullerene SOD mimetic improves cognition and extends the lifespan of mice. Neurobiol Aging 29(1):117–128
119. Kamsler A, Avital A, Greenberger V, Segal M (2007) Aged SOD overexpressing mice exhibit enhanced spatial memory while lacking hippocampal neurogenesis. Antioxid Redox Signal 9 (2):181–189
120. Hu D, Serrano F, Oury TD, Klann E (2006) Aging-dependent alterations in synaptic plasticity and memory in mice that overexpress extracellular superoxide dismutase. J Neurosci 26 (15):3933–3941
121. Serrano F, Klann E (2004) Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res Rev 3(4):431–443
122. Stuhlmeier KM, Li H, Kao JJ (1999) Ibuprofen: new explanation for an old phenomenon. Biochem Pharmacol 57(3):313–320
123. Palayoor ST, Youmell MY, Calderwood SK, Coleman CN, Price BD (1999) Constitutive activation of IkappaB kinase alpha and NF-kappaB in prostate cancer cells is inhibited by ibuprofen. Oncogene 18(51):7389–7394
124. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA (1997) Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. J Biol Chem 272(6):3406–3410
125. Schoonjans K, Staels B, Auwerx J (1996) The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation. Biochim Biophys Acta 1302(2):93–109
126. Weggen S, Erikson J, Das P, Sagi S, Wang R, Pietrzik C, Findlay K, Smith T, Murphy M, Bulter T, Kang D, Marquez-Sterling N, Golde T, Koo E (2001) A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 414(6860):212–216
127. Tegeder I, Pfeilschifter J, Geisslinger G (2001) Cyclooxygenase-independent actions of cyclooxygenase inhibitors. FASEB J 15 (12):2057–2072
128. Zhao W, Payne V, Tommasi E, Diz D, Hsu F, Robbins M (2007) Administration of the peroxisomal proliferator-activated receptor gamma agonist pioglitazone during fractionated brain irradiation prevents radiation-induced cognitive impairment. Int J Radiat Oncol Biol Phys 67(1):6–9
129. Pathan A, Gaikwad A, Viswanad B, Ramarao P (2008) Rosiglitazone attenuates the cognitive deficits induced by high fat diet feeding in rats. Eur J Pharmacol 589(1–3):176–179
130. Kukar T, Prescott S, Eriksen J, Holloway V, Murphy M, Koo E, Golde T, Nicolle M (2007) Chronic administration of R-flurbiprofen attenuates learning impairments in transgenic amyloid precursor protein mice. BMC Neurosci 8:54
131. McGeer PL, McGeer EG (2007) NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging 28(5):639–647
132. Scharf S, Mander A, Ugoni A, Vajda F, Christophidis N (1999) A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. Neurology 53(1):197–197
133. Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, Zalinski J, Cofield M, Mansukhani L, Willson P (1993) Clinical trial of indomethacin in Alzheimer's disease. Neurology 43(8):1609–1611
134. Aisen P, Schafer K, Grundman M, Pfeiffer E, Sano M, Davis K, Farlow M, Jin S, Thomas R, Thal L (2003) Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 289(21):2819–2826
135. Aisen P, Schmeidler J, Pasinetti G, PhD M (2002) Randomized pilot study of nimesulide treatment in Alzheimer's disease. Neurology 58:1050–1054
136. Sainati SM, Ingram DM, Talwalker S, Geis GS (2000) Results of a doubleblind, placebo-controlled study of celecoxib for the progression of Alzheimer's disease. In: Proceedings of the Sixth International Stockholm-Springfield Symposium of Advances in Alzheimer Therapy. p. 180

137. Reines S, Block G, Morris J, Liu G, Nessly M, Lines C, Norman B, Baranak C (2004) Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology 62(1):66
138. Soininen H, West C, Robbins J, Niculescu L (2007) Long-term efficacy and safety of celecoxib in Alzheimer's disease. Dement Geriatr Cogn Disord 23(1):8–21
139. Thal L, Ferris S, Kirby L, Block G, Lines C, Yuen E, Assaid C, Nessly M, Norman B, Baranak C (2005) A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuropsychopharmacology 30(6):1204–1215
140. ADAPT Research Group, Lyketsos C, Breitner J, Green R, Martin B, Meinert C, Piantadosi S, Sabbagh M (2007) Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology 68(21):1800–1808
141. Price JL, Ko AI, Wade MJ, Tsou SK, McKeel DW, Morris JC (2001) Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. Arch Neurol 58(9):1395–1402
142. Stein TD, Johnson JA (2002) Lack of neurodegeneration in transgenic mice overexpressing mutant amyloid precursor protein is associated with increased levels of transthyretin and the activation of cell survival pathways. J Neurosci 22(17):7380–7388