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Treatment of traumatic brain injury with anti-inflammatory drugs

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Abstract

Traumatic brain injury rapidly induces inflammation. This inflammation is produced both by endogenous brain cells and circulating inflammatory cells that enter from the brain. Together they drive the inflammatory response through a wide variety of bioactive lipids, cytokines and chemokines. A large number of drugs with antiinflammatory action have been tested in both preclinical studies and in clinical trials. These drugs either have known anti-inflammatory action or inhibit the inflammatory response through unknown mechanisms. The results of these preclinical studies and clinical trials are reviewed. Recommendations are suggested on how to improve preclinical testing of drugs to make them more relevant to evaluate for clinical trials.

Keywords

Preclinical testing; Clinical trials; Inflammatory mediators; Histology; Brain function

1. Introduction

There are approximately 1.7 million cases of traumatic brain injury (TBI) in the United States annually (Faul et al., 2010). The causes of these TBIs are heterogeneous. Most TBIs are induced by blunt impacts; the remaining result from penetrating or blast injury (Faul et al., 2010). Regardless of how it is induced, TBI ranges in severity that ranges from severe to mild injury. Mild TBI constitutes the vast majority of all TBIs (Faul et al., 2010; Johnson etal., 2015). Regardless of the injury severity, inflammation is an integral part of the pathophysiology of TBI (Finnie, 2013; Johnson et al., 2015). More severe brain injury induces a larger and more prolonged inflammatory response (Kumar and Loane, 2012; Lozano et al., 2015; White et al., 2013; Woodcock and Morganti-Kossmann, 2013). Traumatic injury initiates from a mechanical injury to endothelial cells, neurons, and glia in both clinical TBI and experimental TBI models (Finnie, 2013; Johnson et al., 2015; Kou and VandeVord, 2014; Kumar and Loane, 2012; Woodcock and Morganti-Kossmann, 2013). Damage and death to cells induce extracellular release of a variety of ions, molecules and proteins termed damage-associated molecular patterns (DAMPs) (de Rivero Vaccari et al., 2014). These DAMPs include ATP and K^+, double stranded DNA, and the high mobility group 1 (NMG1) chromatin protein. ATP binds and activates P2X7 receptors and elevated K^+ activates pannexin receptors (Adamczak et al., 2014; de Rivero Vaccari et al., 2014; Kelso

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and Gendelman, 2014). DAMPs bind extracellular receptors that activate intracellular inflammasomes (Adamczak et al., 2014; de Rivero Vaccari et al., 2014; Kelso and Gendelman, 2014). Activated inflammasomes in neurons and astrocytes that process pro-IL-1β and pro-IL-18 into its biologically active forms (Adamczak et al., 2014). Extracellular IL-1β and IL-18 levels rise soon after injury and are key activators of microglia and other early inflammatory events (de Rivero Vaccari et al., 2014; Kelso and Gendelman, 2014). Inflammasomes are also activated following b0069nding of double stranded DNA or HMG1 to cell surface Toll-like receptors (Kelso and Gendelman, 2014; Laird et al., 2014). The release of TNFα, IL-6, IL-12 and interferon γ is an additional early event in inflammatory response (Kelso and Gendelman, 2014). In addition to releasing DAMPs, mechanical injury damages the mitochondria and produces reactive oxygen species and oxidative stress (Cornelius et al., 2013; Rodriguez-Rodriguez et al., 2014). iNOS and NADPH oxidase are additional sources of reaction oxygen species while iNOS produces reactive nitrogen species (Cornelius et al., 2013; Rodriguez-Rodriguez et al., 2014). Pro-inflammatory cytokines, reactive oxygen and reactive nitrogen species interact to increase vascular permeability and damage (Finnie, 2013; Laird et al., 2014; Rodriguez-Rodriguez et al., 2014). Injury results in vasogenic edema and deposition of platelets and polymorphonuclear leukocytes into the brain parenchyma. Vascular changes, infiltration of peripheral inflammatory cells and activation of resident microglia and astrocytes produce more sustained and widespread release of a wide range of cytokines, chemokines, and bioactive lipids (Finnie, 2013; Kou and VandeVord, 2014; Lozano et al., 2015; Woodcock and Morganti-Kossmann, 2013; Ziebell and Morganti-Kossmann, 2010). These early events enhance brain damage, yet they provide the framework for later inflammatory events that enhance tissue repair and remodeling (Kou and VandeVord, 2014; Lourbopoulos et al., 2015; Lozano et al., 2015).

Altering patterns of microglia activation are key events in switching from inflammation with early and largely deleterious effects to a later phase of tissue repair and remodeling (Lourbopoulos et al., 2015; Lozano et al., 2015). This can occur since microglia can differentiate into either pro-inflammatory M1 or an anti-inflammatory M2 phenotypes (Cherry et al., 2014; Hanisch, 2013; Lourbopoulos et al., 2015). M1 microglia enhance inflammation, increase the number of pro-inflammatory cells, and remove apoptotic cells. They produce pro-inflammatory cytokines IL-1β, TNFα. IL-6, and chemokines that recruit additional inflammatory cells to the injury site. M1 microglia enhance oxidative stress through increased NADPH oxidase and iNOS expression (Rodriguez-Rodriguez et al., 2014).

Microglia also differentiate into one of the M2 microglia broadly termed M2a, M2b, and M2c (Cherry et al., 2014; Gensel and Zhang, 2015). All three subtypes of M2 microglia have anti-inflammatory action (Cherry et al., 2014; Gensel and Zhang, 2015). M2a microglia elevate expression of arginase-1, found in inflammatory zone-1 (FIZZ-1), triggering receptor expressed on myeloid cells-2 (TREM2) and IL-1 receptor antagonist and the CD206 mannose receptor (Gensel and Zhang, 2015). M2a microglia suppress inflammation, induce cell proliferation and migration and mediate tissue repair. M2b microglia express toll-like receptors, high levels of arginase-1, IL-1, TNFα, IL-6, and CD86 (Gensel and Zhang, 2015). The role of M2b is not well understood, but they appear to have both pro-and anti-inflammatory activity. M2c microglia also have anti-inflammatory activity that may differ

from M2a microglia. M2c microglia express high levels of TGFβ, CD206, CD163, sphingosine kinase 1 (Gensel and Zhang, 2015). These microglial subsets have been largely defined in vitro (Gensel and Zhang, 2015; Hanisch, 2013). The diversity of in vivo microglial phenotypes is likely to be more complex than in vitro (Cherry et al., 2014; Hanisch, 2013; Lourbopoulos et al., 2015).

The efficacy of anti-inflammatory drugs is directly assessed through changes in the levels of pro- and anti-inflammatory mediators as well as reducing the number and activation state of inflammatory cells. Measurements of inflammatory mediators are difficult since they work at low concentrations and often only act locally in a juxtacrine, paracrine or autocrine manner (Hein and O'Banion, 2009; Kelso and Gendelman, 2014; Lourbopoulos et al., 2015; Woodcock and Morganti-Kossmann, 2013). As a result, preclinical and clinical tests of anti-inflammatory drugs provide only a partial description of the inflammatory mediators produced by brain trauma (Loane et al., 2015; Woodcock and Morganti-Kossmann, 2013; Ziebell and Morganti-Kossmann, 2010) (Tables 2 and 3). Thus it remains poorly understood which inflammatory mediators need to be targeted to get the best therapeutic effect. Examination of the cellular consequences of inflammatory mediators is an alternative to their direct measurement. Microglial or astrocyte activation, immune cell infiltration, BBB breakdown and edema are valuable surrogate markers of early actions of inflammatory mediator after traumatic injury (Finnie, 2013; Loane et al., 2015; Lourbopoulos et al., 2015; Woodcock and Morganti-Kossmann, 2013).

Anti-inflammatory drug action after injury is also assessed indirectly using histological or functional assays (Tables 2 and 3). Mild TBI selectively damages white matter, while more severe TBI damages both gray and white matter (Kou and VandeVord, 2014; Xiong et al., 2013). Histological damage occurs rapidly after TBI and can evolve for days to weeks after injury (Xiong et al., 2013).

Anti-inflammatory drugs have been tested in a variety of experimental TBI models. TBI animal models can be divided into closed head injury models in which the skull remains intact before, and open head injury models in which brain injury occurs through a craniotomy (Johnson et al., 2015; Xiong et al., 2013). The most common closed head model injury drops a weight on the skull. Weight drop produces a focal injury that damages the cortex and underlying hippocampus. A midline impact produces a focal TBI while a lateral impact produces a TBI that is more diffuse. Marmarou's weight drop differs from other weight drop models by affixing a metal helmet to the head of the rodent prior to dropping the weight. Marmarou's weight drop model produces a diffuse TBI.

The two common open head injury models are fluid percussion and controlled cortical impact (Johnson et al., 2015; Petraglia et al., 2014). Controlled cortical impact produces a focal injury in the cortex at the site of impact. More severe impacts may damage the underlying hippocampus as well. White matter injury following controlled cortical impact is more diffuse than gray matter injury (Johnson et al., 2015). Fluid percussion produces a more diffuse gray and white matter injury than controlled cortical impact (Johnson et al., 2015; Petraglia et al., 2014). Fluid percussion and controlled cortical impact produces a more uniform injury than closed head models (Johnson et al., 2015). A few studies cited in

this review use a cryogenic lesion model that produces a highly focal injury. Cryogenic models produce a lesion that differs more from clinical TBI than other animal TBI models (Xiong et al., 2013).

Assessment of neurological reflexes or motor function is commonly an outcome measure used to assess the therapeutic action of antiinflammatories (Johnson et al., 2015). Anxious or depressive-like symptoms are frequently assessed as well (Petraglia et al., 2014). Many studies also use behavioral tests of cognitive function or memory. Neurological severity score is the most common, easy and rapid assessment of neurological reflexes and motor skills. Rotarod, beam balance, inclined plane and foot fault are also commonly used tests of motor skills (Petraglia et al., 2014). Motor deficits arise soon after injury (Xiong et al., 2013). Anti-inflammatory drugs limit motor deficits in multiple TBI models (Tables 2 and 3). Most models, however, produce transient deficits in reflexes and motor skills that recover spontaneously within one week. Thus, the assessment of drug efficacy using reflexes or motor deficits has the caveat that the anti-inflammatory drug is, at best, improving recovery rate. In contrast to reflex and motor deficits, deficits in cognition and memory can be permanent (Xiong et al., 2013). Common cognitive and memory tests include: novel object recognition, Y-maze, Barnes maze, Morris water maze, and active place avoidance. Experimental TBI can induce anxious or depressive-like behavior in rodents that model for changes in affective state that commonly occur after clinical TBI (Petraglia et al., 2014). Common tests of anxiety include open field and elevated plus maze while depressive-like behavior can be assessed using the forced swim, tail suspension or sucrose/saccharin preference tests (Petraglia et al., 2014). Cognitive or affective test often require the animal to move, so it is necessary to postpone testing animals until it is known that motor deficits have recovered. Otherwise, impaired motor function can give a false positive result on cognitive and affective testing. Anti-inflammatory drugs limit long-lasting cognitive and affective impairment (Tables 2 and 3). Improved cognition and affect produced by anti-inflammatory drugs constitute a de novo recovery rather than simple increase of the rate of recovery.

This review divides anti-inflammatory drugs to treat TBI into two groups; those that inhibit the inflammatory response through known mechanisms (Table 2) and those whose anti-inflammatory mechanism are unknown (Table 3). Studies were only included if the drug had a known anti-inflammatory action or altered an inflammatory outcome. An advantage of investigating drugs with known-anti-inflammatory action is that the studies more readily tells us about which inflammatory mediators are potentially targets for therapeutic intervention than drug studies in which the anti-inflammatory action is unknown. Studies of drugs with an unknown anti-inflammatory action were not included if an inflammatory outcome was not assessed. The results section focuses on individual drugs that have been examined in many studies; the relevant outcomes of drugs evaluated in one or two studies are summarized in Tables 2 and 3. Tables 2 and 3 also provide the time to 1st dose after injury for each study. This is a key parameter of the utility of a drug in a clinical trial since many hours are needed and patients are difficult to enroll in clinical trials (Loane et al., 2015). Traumatic injury evolves over time so Tables 2 and 3 also provide the time after injury when inflammatory, histological and functional tests are performed (Woodcock and Morganti-Kossmann, 2013). Earlier studies in this review assessed microglial activation using pan-microglial markers (Iba-1, Cd11b, F4/80) prior to the development of markers that

distinguish M1 and M2 microglia (Cherry et al., 2014; Hanisch, 2013) (Tables 2 and 3). In addition none of the microglial markers used by the studies cited in this review distinguish between resident microglia and macrophages that infiltrated into the brain after injury. Studies that only use pan-microglial markers cannot conclude whether a drug has an anti-inflammatory or pro-inflammatory effect on microglia (Cherry etal., 2014; Lourbopoulos et al., 2015). Other studies measure inflammatory mediators specific for M1 (iNOS) or M2 (IL-10) without discussing the how the drug modulated microglial activation. A careful analysis of microglial subsets is needed to understand how anti-inflammatory drugs limit traumatic brain injury (Cherry et al., 2014; Hanisch, 2013). Tables 2 and 3 indicate which antigenic markers were used to analyze microglia to give better information about the action of a given drug on microglia. Finally, this review examines the clinical trials of drugs that have shown anti-inflammatory action in preclinical testing.

1.1. Drugs with known anti-inflammatory action

1.1.1. Glucocorticoids—Glucocorticoids have broad anti-inflammatory action. They inhibit synthesis of interleukins and bioactive lipids, suppress cell-mediated immunity, decrease leukocytes number and activity (Alderson and Roberts, 2005). The strong anti-inflammatory action of glucocorticoids made them some of the first drugs tested against experimental TBI. When first dosed 5 min post injury in rats, dexamethasone decreased microglial numbers at 1 and 3 days with no effect at 4 and 6 days (Zhang et al., 2008; Zhang et al., 2007). At 5 days post-injury, microglial activation was inhibited at the contusion area and overall brain edema was reduced (Holmin and Mathiesen, 1996). First dosing at 5 min decreased IL-16 expression at one and two, but not at day 4 (Zhang et al., 2008). Treatment with dexamethasone 4 h after weight drop, increased the number of degenerating neurons at the impact site at 5 and 14 days post-injury (Gahm et al., 2005). Apoptosis at the impact site also increased 5 days post-injury. None of these studies examined whether the anti-inflammatory action of dexamethasone resulted in improvement in brain function (Table 2). The strong anti-inflammatory effect of dexamethasone when given immediately after injury was no longer present when dosed 4 h after injury (Gahm et al., 2005). This narrow therapeutic window likely contributed to the failure of corticosteroids in clinical trials (Roberts et al., 2004).

1.2. Non-steroidal anti-inflammatory drugs (NSAIDS)

NSAIDS are a family of drugs with potent analgesic and anti-pyretic actions. NSAIDS also have anti-inflammatory activity through inhibition of COX-1 and COX-2 (Hein and O'Banion, 2009). COX-1 and COX-2 become active soon after TBI and begin to synthesize prostaglandins (Hein and O'Banion, 2009). Some NSAIDS inhibit both COX-1 and COX-2; others more specifically inhibit COX-2 (Hein and O'Banion, 2009). Both types of NSAIDs have been tested in animal models of TBI (Table 2). Indomethacin and ibuprofen inhibit COX-1 and COX-2 (Chao et al., 2012; Girgis et al., 2013). When either dosed prior to or 10 min post-injury, indomethacin and ibuprofen show a strong anti-inflammatory effect by inhibiting IL-1β, IL-6, IL-10 and prostaglandins (Chao et al., 2012; Girgis et al., 2013; Keshavarzi et al., 2012). Depending upon the model, there were mixed results concerning edema (Chao et al., 2012; Girgis et al., 2013). Indomethacin and ibuprofen had little effect

improving brain function when dosed alone or in combination with Vitamin E (Chao et al., 2012; Clond et al., 2013; Girgis et al., 2013) (Table 2).

COX-2 selective drugs (Carpofen, Celecoxib, Meloxicam, Nimesulide and Roficoxib) were tested in a variety of animal models of TBI. All studies dosed the COX2-selective inhibitors either before injury or within 30 min post-injury (Table 2). Carpofen and Celecoxib inhibited IL-1β with no effect on the anti-inflammatory cytokine IL-10 (Dash et al., 2000; Thau-Zuchman et al., 2012). Meloxicam and Nimesulide prevented prostaglandin production (Girgis et al., 2013; Hakan et al., 2010). Carprofen also inhibited microglial activation at 4 h post-injury (Thau-Zuchman et al., 2012). Nimesulide had no effect on edema, and there was no clear result of Meloxicam on edema (Girgis et al., 2013; Hakan et al., 2010). Rolicoxib, when dosed 5 min after injury had no effect on hippocampal neuronal loss (Kunz et al., 2006). Like the less specific NSAIDS, the more specific COX-2 inhibitors showed little ability to improve brain function (Table 2). Taken together, these studies suggest that NSAIDs produce anti-inflammatory activity against experimental TBI, but this anti-inflammatory effect is not sufficient to prevent tissue damage and functional impairments. These studies argue against targeting COX1 or COX2 is unlikely to be an effective treatment for TBI.

1.3. TNFα inhibitors

TNFα is potent pro-inflammatory cytokine that is rapidly induced by traumatic injury (Chio et al., 2010; Lozano et al., 2015; Woodcock and Morganti-Kossmann, 2013). HU-211 is a synthetic cannabinoid that lacks cannabinoid activity yet inhibits production of TNFα and is a non-competitive NMDA receptor antagonist (Shohami et al., 1997; Shohami et al., 1995). When dosed 1 h after injury, HU-211 produced long-term improvements in Morris water maze or beam walking or balancing. When dosed up to 2 h after injury, HU-211 limited edema and improved BBB when dosed up to neurological severity score when dosed up to 4 h (Shohami et al., 1997; Shohami et al., 1995). Two additional potent TNFα antagonists are Eternercept, and 3,6'-dithiothalidomide (Chio et al., 2010). Etanercept is a decoy receptor consisting of a human α receptor dimer fused to human IgG1 that interferes with TNFα binding to cell surface TNFα receptors (Chio et al., 2010). When administered 5 min after injury, Etanercept decreased IL-1β and IL-6 at 3 days post-injury and decreased TNFα at both 3 and 7 days post-injury (Chio et al., 2013). These cytokine changes likely underlie the reduced astrocytic and microglial activation seen 3 day postinjury. Decreased neuronal and astrocytic apoptosis and smaller lesion volume were also reported. Treated mice had improved reflexes and motor function when tested up to 7 days post-injury (Cheong et al., 2013). Synthesis of TNFα is inhibited by 3,6'-dithiothalidomide (Baratz et al., 2011). When dosed 1 h prior to injury, 3,6'-dithiothalidomide-treated mice preformed better on Y-maze, novel object recognition and passive avoidance 3 and 7 days post-injury (Baratz et al., 2011). These studies provide evidence that early antagonism of TNFα is therapeutic. Mice treated with 3,6'-dithiothalidomide had similar performance on Y-maze and novel object recognition as those treated 1 h after injury. This therapeutic effect was absent when 3,6'-dithiothalidomide was dosed 18 h after injury.

1.4. Interleukin 1 inhibitors

Like TNFα, IL-1β is a potent proinflammatory cytokine whose expression increases rapidly after injury (Finnie, 2013; Kumar and Loane, 2012). Rodents and humans regulate IL-1 action using an endogenous IL-1ra that is a decoy receptor for IL-1β (Tehranian et al., 2002). Mice engineered to overexpress IL-1ra had less edema one-day postinjury and improved neurological scores between 1 and 14 days post-injury (Tehranian et al., 2002). IL-1β, TNFα and IL-6 expression at 6 h post-injury was elevated in the overexpressing as compared to wild-type mice. This study provided an important proof-of-principle that early targeting of IL-1β is therapeutic in treating TBI. Administering IL-1ra within 5 min of injury resulted in improved histology and motor skills assayed within 3 days post injury (Jones et al., 2005). Administration at 15 min after injury improved histological outcomes yet showed minimal improvements in reflexes or motor impairments (Knoblach and Faden, 2000; Sanderson et al., 1999). Dosing of anakinra (recombinant human IL-1ra) two hours after experimental TBI had little effect on lesion volume, rotarod, or Morris water maze (Anderson et al., 2013). The poor performance of anakinra on functional outcome when dosed at two hours post injury is notably different than the studies that dosed IL-1ra soon after injury (Jones et al., 2005; Knoblach and Faden, 2000; Sanderson et al., 1999) These limited preclinical studies suggest that drugs based upon IL-ra may have too narrow a therapeutic window to effective in a clinical trials. In a phase II randomized control clinical trial, dosing Anakinra within 24 h of injury modulated the neuroinflammatory response, but the study was too small to determine if Anakinra had a therapeutic effect (Helmy et al., 2014).

1.5. Phosphodiesterase inhibitors

Phophodiesterase inhibitors limit the breakdown of the second messenger cyclic AMP to 5'AMP. The transient increase of cAMP levels following experimental TBI provided a rationale to study a therapeutic effect of phosphodiesterase inhibitors. Rolipram, a specific inhibitor of phosphodiesterase IV, improves both histology and function when dosed 30 min before injury (Atkins et al., 2013). Pre-injury treatment with Rolipram lowered IL-1β and TNFα levels 3 h after injury (Atkins et al., 2007). Dosing Rolipram 30 min after injury produced a similar reduction of IL-1β and TNFα levels 3 h after injury yet lesion size was increase over vehicle controls (Atkins et al., 2012). These data suggest that a simple reduction of a few pro-inflammatory cytokines is not predictive of a favorable histological outcome. Multiple isoforms of phophodiesterase are present in the brain; the expression of these isoforms changes rapidly after experimental TBI (Oliva et al., 2012). Thus, Rolipram is inhibiting a different spectrum of phosphodiesterases depending upon time to first dose after injury. More specific phosphodiesterase inhibitors may limit the adverse effects of post-treatment Rolipram.

1.6. Drugs with unknown anti-inflammatory action

1.6.1. Minocycline—Minocycline is a lipophilic member of the tetracycline family of antibiotics that penetrates the BBB (Garrido-Mesa et al., 2013). At concentrations higher than needed for anti-microbial action, minocycline has anti-inflammatory activity (Garrido-Mesa et al., 2013). Seven studies from multiple laboratories have established the ability of

minocycline to limit neuroinflammation after brain injury (Table 3) (Abdel Baki et al., 2010; Adembri et al., 2014; Haber et al., 2013; Homsi et al., 2009; Sanchez Mejia et al., 2001; Siopi et al., 2011, 2012). Dosing of minocycline between 5 min and 1 h after injury improved performance on a variety of behavioral tasks including novel object recognition, elevated plus maze, Morris water maze and active place avoidance (Abdel Baki et al., 2010; Adembri et al., 2014; Haber et al., 2013; Siopi et al., 2012). Minocycline dosed orally 2 h after injury, however, did not improve deficits on the Morris water maze (Vonder Haar et al., 2014). Minocycline has been shown to inhibit microglial activation using antibodies that recognize an array of antigenic markers for different microglial subpopulations (Adembri et al., 2014; Haber et al., 2013; Kelso et al., 2011; Siopi et al., 2011; Vonder Haar et al., 2014). Lowered production of IL-1β likely underlies the inhibitory action of Minocycline on microglia (Homsi et al., 2010). Minocycline prevents injury to both gray matter (Adembri et al., 2014; Sanchez Mejia et al., 2001; Vonder Haar et al., 2014) and white matter (Abdel Baki et al., 2010; Siopi et al., 2011). Drug combinations with minocycline have also been examined. Combining minocycline with the anti-oxidant melatonin yielded little therapeutic benefit (Kelso et al., 2011). In contrast, positive drug synergy arose from combining minocycline with a second antioxidant, N-acetylcysteine. The combination of minocycline and N-acetylcysteine synergistically improved memory in an active place avoidance task. Even though minocycline is a potent inhibitor of microglial activation, Minocycline plus N-acetylcysteine synergized to both induce and modulate microglial activation (Abdel Baki et al., 2010; Haber et al., 2013). A major caveat of these studies is that all but one of these studies dosed minocycline between 5 min and 1 h. Thus it remains uncertain if minocycline retains sufficient potency when dosed in a clinically relevant therapeutic window.

1.7. Progesterone

Progesterone is a gonadal hormone that has multiple anti-inflammatory actions (Wei and Xiao, 2013). After an initial dose 1 h after injury, progesterone inhibited IL-1β at 4 h post-injury, and TNFα at 12 post-injury (He et al., 2004). When dosed 30 min after injury, progesterone first increased IL-1β levels at 6 h yet lowered levels at 24 h. IL-6 was inhibited at both 6 and 24 h post-injury. Progesterone decreased TNFα at 6 h post-injury and increased TGFβ levels 24 h after injury (Sarkaki et al., 2013). Dosing progesterone 1 h after injury inhibited a large number of inflammatory mediators (1L-1 receptor 1,1L-6 TNFα, CxCL10, Toll-like receptor 2, Toll-like receptor 2, CCL2, COX-2, iNOS, NF-κB and complement factors 3 and 5) (Cutler et al., 2007; Hua et al., 2011; Si et al., 2014). IL-6 and Cox-2 levels remained inhibited 3 days post-injury and NF-κB activation remained inhibited at 7 days post-injury (Cutler et al., 2005, 2007). Progesterone inhibited astrocyte activation 1 day post-injury (Cutler et al., 2007; Pettus et al., 2005). Despite its strong anti-inflammatory action, progesterone had inconsistent effects on edema (Cutler et al., 2005; Khaksari et al., 2011; Kumasaka et al., 2014). Multiple laboratories showed prevention of gray matter injury and apoptosis (Cutler et al., 2005, 2007; Si et al., 2014; Tang et al., 2013). Multiple studies showed that progesterone results in improved functional outcome. Injured rats dosed with progesterone 1 h postinjury had, less anxiety-like behavior on the open field test and elevated plus maze, and improved recovery of motor function (Cutler et al., 2005, 2007). One study showed improvement in Morris water maze (Tang et al., 2013), while two studies showed that progesterone did not improved acquisition on the Morris water maze; one study

claimed that there was improvement in the search strategy utilized despite the rats not learning the location of the target platform (Djebaili et al., 2005; Tang et al., 2013). When considered together, these studies strongly suggest that progesterone has long-lasting and widespread anti-inflammatory action that promoted functional recovery of the brain, when dosed 1 h after injury. A caveat of these studies is that it remains unknown if progesterone has similar potency when dosed later than 1 h since one-hour therapeutic window has limited value in treating clinical TBI. Progesterone showed some efficacy in clinical trials when dosed up to 11 h after injury (Xiao et al., 2008).

Dosing progesterone 4 h after injury altered expression of a large number of mRNAs at 72 h post-injury (Anderson et al., 2011). Many of these genes did not function as inflammation regulators (Anderson et al., 2011). Expression changes in genes that modulate inflammation included the complement system (C1qa, C1qC, C1s1s and C3), chemokines and their receptors (CCl12; CCl17; CCR receptor 1; CCR receptor 5), and synthesis of bioactive lipids (Phospholipase A2, COX 2). Transcripts levels increased ofIL-1ra, the pro-inflammatory cytokine IL-18, caspases 4 and 8 and GFAP. Surprisingly, dosing progesterone at either 1 or 4 h post-injury had did not alter IL-1β and TNFα mRNA despite the findings decreased levels of IL-1β and TNFα protein (He et al., 2004; Hua et al., 2011; Sarkaki et al., 2013). Despite this wealth of genetic information about the effect of progesterone on gene expression, little is known whether progesterone retains its anti-inflammatory or therapeutic action when dosed at 4 h post-injury.

1.8. Erythropoetin

Erythropoietin controls proliferation of erythrocyte precursors in bone marrow. When tested in a variety of animal models of TBI and stroke, erythropoietin has anti-apoptotic, anti-oxidative, angiogenic, and neurotrophic activities (Radosevich et al., 2013; Sargin et al., 2010). Fewer studies have examined anti-inflammatory activity of erythropoietin. When dosed 5 min after injury, erythropoietin lowered IL-1β, IL-6 and CXCL2 (Bian et al., 2010; Lieutaud et al., 2008). When dosed 1 h post-injury, erythropoietin also inhibited IL-1β, NF-κB and TNFα and complement C3, without altering IL-6 levels (Chen et al., 2007a). One-hour dosing also blocked astrocyte, but not microglial activation (Chen et al., 2007a). One-hour dosing prevented injury to gray matter and axons (Chen et al., 2007a; Meng et al., 2011; Yatsiv et al., 2005) and improved reflex and motor impairments on NSS and open field but not rotarod (Meng et al., 2011; Yatsiv et al., 2005). Rotarod has a higher demand on the motor system than open field or NSS (Xiong et al., 2013). One-hour dosing of erythropoietin improved performance on the novel object recognition test (Yatsiv et al., 2005). Hellewell et al. showed that one-hour dosing of erythropoietin prevented increased IL-1β and microglia later after injury in a model that combined weight drop and hypoxia (Hellewell et al., 2013). In this study, erythropoietin limited gray and white matter damage. Meng et al. report that dosing of erythropoietin at one-day post-injury improved motor and cognitive performance one month later (Meng et al., 2011). This suggests that erythropoietin produced long-lasting improvements that are likely permanent.

1.9. Statins

The statin drug family inhibits the rate-limiting enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase (Radosevich et al., 2013). Modulation of lipid synthesis by lowering mevalonic acid levels underlies the anti-inflammatory activity of statins. Mevalonic acid is needed for protein prenylation that is believed to underlie the anti-inflammatory action of statins (Devaraj et al., 2006). When dosed 1 h post-injury, simvastatin inhibited expression of TLR4, NF-κB, IL-1β, IL-6, TNFα, and ICAM-1 at 24 h post-injury (Chen et al., 2009). At 24 h post-injury, simvastatin inhibited neutrophil infiltration, edema and BBB breakdown (Chen et al., 2009). One-hour dosing of simvastatin lowered cortical apoptosis and improved performance on rotarod (Chen et al., 2009). When dosed at 2 h post-injury, simvastatin altered expression of a large number of transcripts encoding COX2 IL-18, IL-1ra, and a large number of chemokines (Vonder Haar et al., 2014). Despite these changes in gene expression, two-hour dosing of simvastatin had no effect on lesion size, performance on rotarod or Morris water maze (Vonder Haar et al., 2014). When dosed one-day postinjury, simvastatin retained its anti-inflammatory activity by inhibiting IL-1β, TNFα, or IL-6 (Li et al., 2009). Microglia and astrocyte activation were also limited at 3 days post-injury (Li et al., 2009). Dosing simvastatin beginning at one day had no effect on mNSS until 35 days postinjury, when a small, but significant improvement was noted (Li et al., 2009). The ability of atorvastatin and lovastatin was also assessed in their ability to limit experimental TBI. Atorvastatin, when given 30 min after injury, inhibited microglial activation between 1 and 7 days post-injury and lowered IL-6, TNFα, eNOS levels between 2 h and 3 days post-injury (Wang et al., 2007). Atorvastatin protected against hippocampal neuronal loss, improved performance on the rotarod at 5 days post-injury and on the Morris water maze 25 days post-injury (Wang et al., 2007). Lovastatin and atorvastatin also had therapeutic effects when first dosed many days prior to injury (Chen et al., 2007b; Wang et al., 2007). Taken together these data suggest that, when dosed within 1 h after injury, statins showed a strong antiinflammatory effect and improved brain function. When dosed later, statins retain their anti-inflammatory action yet become less effective in preventing behavioral deficits.

1.10. N-acetylcysteine

In addition to its better-known action as an anti-oxidant, N-acetylcysteine can act as an anti-inflammatory drug. When dosed 5 min after injury, N-acetylcysteine inhibited NF-κB, IL-1β, TNFα, IL-6, edema and breakdown of the blood brain barrier three days after injury (Chen et al., 2008). Redox-dependent inhibition of NF-κB is a potential mechanism of the anti-inflammatory action of N-acetylcysteine (Chen et al., 2008). In contrast, when dosed 3 h prior to injury, N-acetylcysteine had no effect on IL-1β levels measured one-hour post injury (Abdel Baki et al., 2010). N-acetylcysteine dosed 1 h after injury had no effect on microglial activation or acquisition of an active place avoidance task (Haber et al., 2013). These data argue for additional preclinical testing of N-acetylcysteine. In a phase II clinical trial, N-acetylcysteine did show positive effects even when dosed 72 h after injury (Hoffer et al., 2013).

1.11. Clinical trials of drugs with anti-inflammatory action

1.11.1. Erythropoietin—Anemia commonly arises in patients with severe TBI. Anemias can be treated either by erythropoietin or by blood transfusion. Erythropoietin was compared with high or low hemoglobin transfusion in 200 patients with a closed head injury having a Glasgow Coma Score > 3 (Robertson et al., 2014). Treatment was initiated within 6 h after injury. Patients were transfused to maintain a hemoglobin threshold of 7 or 10 g/dl and either received erythropoietin or placebo. The primary outcome was at 6 months post-injury. Glasgow Outcome Score did not differ in patients who received erythropoietin or placebo. Glasgow Outcome Score did not improve regardless if hemoglobin levels were maintained at 7 or 10 g/dl. Mortality was similar in all groups. In an observational trial, one hundred and fifty patients with blunt impact and penetrating TBI classified moderate to severe (Abbreviated Injury Score 3–5) were divided into a group that received erythropoietin and a control placebo group (Talving et al., 2012). Erythropoietin therapy was first given within the first 2 weeks of injury. Patients who received erythropoietin had significantly longer stays in the intensive care unit. These longer stays likely reflected the lower mortality of the erythropoietin group while in the hospital when compared to patients receiving placebo. In a third trial, 11 blunt impact TBI with an admission Glasgow Coma Score < 13 were treated with erythropoietin within 6 h after injury (Nirula et al., 2010). Five patients constituted a control group. Intracerebral pressure was measured and venous blood was collected at the time of injury and at daily intervals until 5 days. Plasma levels of the brain injury biomarkers S100b and neuronal-specific enolase were measured. No significant differences were seen in biomarker levels or intracerebral pressure. Taken together, these studies provide little justification to test erythropoietin in a phase III trial.

1.12. Anakinra

A phase II randomized control clinical trial studied whether subcutaneous injection of Anakinra, a recombinant human IL-1ra entered the brain. Alterations of the neuroinflammatory response by Anakinra after traumatic brain injury was also examined (Helmy et al., 2014). Twenty patients were enrolled with a Glasgow Coma Score of ≤ 8 and a predominantly diffuse injury. All patients were recruited in the first 24 h after injury. After an initial period of 6 h, to provide a monitoring baseline, 10 patients received 5 daily doses of Anakinra and 10 patients received an equivalent dosing of placebo. Microdialysis probes were inserted into radiologically normal brain parenchyma consistent with diffuse brain injury. The dialysate was sampled 20 times at 6-hour intervals during the 5-day period and tested for IL-1ra and 42 additional cytokines and chemokines. IL-1ra levels were significant higher in patients that received Anakinra than placebo. CCL22 levels were significantly lowered in the Anakinra group. Heterogeneity in the inflammatory response and the relatively few patients likely underlie why few of the 42 inflammatory mediators tested was altered by this potent antiinflammatory drug. The present study was too small to establish whether Anakinra had any beneficial therapeutic effect on clinical outcome. This study also suggests that the extracellular fluid in the brain is a more biologically relevant compartment to study of cytokines than plasma or CSF.

1.13. Statins

Two small drug trials and two large observational trials have examined the therapeutic efficacy of statins for TBI. Twenty-one patients with moderate to severe TBI (GCS score < 13) were divided into a group of 8 patients treated with rosouvastatin and a placebo group of 13 patients (Tapia-Perez et al., 2008). The first dose of rosouvastatin was given within the first 24 h after TBI. Venous blood was collected on admission and 3 days later. The primary outcome was assessment of amnesia and disorientation by the Galveston Orientation Amnesia Test. At 120 days after injury, 2 patients in both the rosouvastatin and placebo groups had a negative Galveston Orientation Amnesia Test suggesting little or no effect. A secondary outcome was the assessment of plasma levels of TNFα, IL-1β, and IL-6 at time of admission and 3 days later. Rosuvastatin had no effect on TNFα, IL-1β, and IL-6 levels. Both groups had similar disability outcomes when assessed at three months. A second trial by the same group studied anti-inflammatory effects of rouvastatin in 36 patients with moderate to severe TBI (GCS score < 13) (Sanchez-Aguilar et al., 2013). Within 24 h of injury, nineteen patients were receiving rosuvastatin and 17 were receiving placebo. Plasma TNFα, IL-1β, IL-6, and IL-10 were assessed 72 h after injury. TNFα was significantly lowered by rosuvastatin. In contrast, rosuvastatin had no effect on IL-1β levels but trended to lower IL-6 and IL-10 levels. Patients also received the Galveston Orientation Amnesia Test and the Disability Rating Scale upon discharge from the hospital and 3 and 5 months after TBI. The placebo and rosuvastatin group did not significantly differ on these two tests at any of the three time points.

An observational study by Efron et al., examined 1224 patients aged 65 or older with moderate to severe TBI (Abbreviated Injury Score of ≥3). At the time of injury, 21.1% were taking statins (Efron et al., 2008). Preinjury statin treatment was associated with reduced inhospital mortality. This effect was only observed in patients who did not have preexisting cardiovascular disease. Schneider et al. performed an observational study of 523 patients with moderate to severe TBI (Abbreviated Injury Score of ≥3) (Schneider et al., 2011). Of these 22% had ongoing use of statins. These patients had a lower risk of in-hospital death. At one year assessment of Extended Glasgow Outcome Scale of the 264 remaining patients showed that statin users had a small, but significantly higher likelihood of good recovery. This therapeutic effect of statins, however, was abolished by cardiovascular comorbidities in the group using statins.

1.14. Progesterone

Progesterone has recently been studied in two large phase II clinical trials. A randomized, placebo-controlled trial of progesterone was performed on 159 patients with a Glasgow Coma Score ≤ 8 (Xiao et al., 2008). Patients were treated within 8 h of injury. The Glasgow Outcome Scale, Independence Measure score and mortality were measured at 3 and 6 months. The progesterone-treated group had significantly better Glasgow Outcome and Independence Measure scores than the placebo group at 3 months and 6 months. The progesterone group also had a significantly lower mortality rate than the placebo group at 6 months.

The PROtect phase II enrolled seventy-seven patients in a group to receive progesterone or 23 patients to receive placebo within 11 h of injury (Wright et al., 2007). Both groups had a Glasgow Coma Scale score of 4 to 12 at admission. Mortality and Glasgow Outcome Scale-Extended was assessed 30 days post-injury. Patients began progesterone treatment 6.3 ± 2.1 h after injury. Patients receiving progesterone had a lower 30-day mortality rate than controls. Patients with moderate traumatic brain injury had better outcomes on the Glasgow Outcome Scale-Extended test and Disability Rating Scale. Patients receiving progesterone with severe traumatic brain injury showed no significant benefit. These studies provided justification for the large multi-center Phase III PROtect III trial. PROtect III examined whether progesterone produced a more favorable functional recovery as compared to placebo using the Extended-Glasgow Outcome Score 6 months post injury (Wright et al., 2014). Progesterone was first dosed within 4 h post-injury. The study was terminated after no significant effect was observed in 882 patients. A second trial (SYNAPSE) examined progesterone in 569 when dosed to severe TBI patients (Glasgow Coma Score < 8) (Skolnick et al., 2014). Progesterone was first administered 8 h after injury. The primary outcome was the improvements in the Glasgow Outcome Score at 6 months. Secondary outcomes were improvements in Glasgow Outcome Score at 3 months, reduced mortality at 1 and 6 months and the Extended-Glasgow Outcome Score at 6 months. Progesterone did not differ from control in any of the outcomes. Together these two studies suggest little benefit from acute administration of progesterone to treat moderate to severe TBI.

1.15. Methylprednisolone

Corticosteroids have been used to treat head injuries for many decades. In 1997, a meta-analysis of a large number of small trials suggested that corticosteroids produced a small decrease in the risk of death (Alderson and Roberts, 1997). This finding prompted a large phase III trial (CRASH, corticosteroid randomization after significant head injury) that enrolled 10,008 adults with TBI and a Glasgow Coma Score (GCS) ≤ 14 (Roberts et al., 2004). Within 8 h of injury, these patients received a 48 h infusion of methylprednisolone or placebo. At 2 weeks of injury, mortality was assessed and death or disability at 6 months. The methylprednisolone group had a greater death risk than placebo regardless of the injury severity.

1.16. Etanercept

The TNFα antagonist, etanercept has been administered perispinally to treat back pain and sciatica (Tobinick, 2010). Tobrick et al. followed twelve patients with chronic neurological dysfunction after TBI that were treated with etanercept. Etanercept treatment was initiated, on average, 115 months post-injury (Tobinick et al., 2012). Patients were assessed immediately, 1 week and 3 weeks after etanercept dosing for improved motor, cognitive, sensory psychological functioning. The patients showed improvements in many of the parameters of motor, cognitive, sensory psychological functioning at all three time points. This study is very provocative given the very long time to first dosing, and that etanercept provided both immediate and long-term improvement (Tobinick et al., 2012). These findings could be readily tested in animal models of TBI. The two preclinical studies of etanercept only examined dosing immediately after injury. Additional studies are warranted dosing etanercept much longer after injury (Cheong et al., 2013; Chio et al., 2013).

1.17. N-acetyl cysteine

The safety and potential therapeutic efficacy of N-acetyl cysteine was assessed in 41 soldiers who had a mild blast-induced TBI (Hoffer et al., 2013). Patients receiving N-acetyl cysteine were subdivided into a group first dosed 24 h after injury and a second group first dosed at 26–72 h after injury. At one week, drug efficacy was determined by improvements in the number of neurological symptoms and improved performance on neuropsychological testing. The group receiving N-acetyl cysteine before 24 h after injury reported better alleviation of neurological symptoms and improved neuropsychological performance than a placebo-treated group. Dosing N-acetyl cysteine between 24 and 72 h after injury reduced neurological symptoms but did not improve outcomes on neuropsychological tests. Thus, N-acetyl cysteine showed higher efficacy when dosed earlier after injury.

2. Discussion

Inflammation initiates soon after traumatic brain injury (Finnie, 2013). Brain damage is greatly limited if anti-inflammatory drugs are dosed prior to or soon after experimental TBI (Tables 2 and 3). These studies have shown the important proof-of-principle that TBI can be limited by targeting neuroinflammation. Dosing of a large number of anti-inflammatory drugs soon after injury produces a large therapeutic effect. These data suggest that neuroinflammation makes a large contribution to traumatic brain damage (Tables 2 and 3). Dosing soon after injury results in a large beneficial response regardless if the drug has a narrow or broad anti-inflammatory action. This suggests that there are many potential targets to limit injury early in the inflammatory process.

Unfortunately, it is not feasible to conduct a clinical trial with dosing an anti-inflammatory drug either before or within 1 h after TBI. Most anti-inflammatory drugs have not been dosed at later times after injury. The therapeutic efficacy of dexamethasone, minocycline, and simvastatin has been assessed when first dosed at various time after injury (Tables 2 and 3). Increasing the interval between injury and first dose greatly lowered the therapeutic efficacy of these drugs. Erythropoietin is the exception that retained a substantial therapeutic action when dosed one day post-injury (Meng et al., 2011). It is unclear if erythropoietin retained anti-inflammatory activity when dosed 1 day after injury because there were no inflammatory outcomes measured in this study. Erythropoietin showed no therapeutic efficacy in a clinical trial that dosed the drug within 6 h after injury. In one study treatment with the peptide TSG-6 improved inflammatory, histological and functional outcomes when dosed 6 h after injury (Watanabe et al., 2013). Thus, it appears that therapeutic window of anti-inflammatory drugs may be a major hurdle to developing them as effective drugs to treat traumatic brain injury.

Drug development should also consider many important pharmacology parameters other than therapeutic window. These include potential routes of administration, total number of doses, therapeutic index and adverse effects. These additional pharmacological parameters are available for some, but not all the drugs summarized in Tables 1 and 2.

The levels and actions of neuroinflammatory mediators change rapidly after TBI (Kumar and Loane, 2012). We have some knowledge of how to target these early inflammatory

mediators (Tables 2 and 3). There are relatively few studies that dose drugs at longer intervals after injury, therefore little is known about which mediators are effective drug targets hours to days after TBI. Our need for a deeper understanding of inflammation is evident in two studies examining the efficacy of the phophodiesterase inhibitor, Rolipram. When dosed either before or 30 min post-injury, Rolipram had similar effect of the levels of two central mediators central to inflammation, IL-1β and TNFα (Atkins et al., 2012; Atkins et al., 2007). Pretreatment improved a variety of histological outcomes while post-treatment worsened many of the same outcomes (Atkins et al., 2012; Atkins et al., 2007). Rolipram improved functional outcomes when dosed 2 weeks after injury, but it is uncertain whether this improvement was due to any anti-inflammatory action of the drug (Atkins et al., 2012; Atkins et al., 2007). Multiple isoforms of phophodiesterase are present in the brain; the expression of many isoforms rapidly changes after experimental TBI (Oliva et al., 2012). Thus, Rolipram is inhibiting a different spectrum of phosphodiesterases depending upon time to first dose after injury. More specific phosphodiesterase inhibitors may limit the adverse effects of post-treatment Rolipram.

Wide scale analysis of transcriptional changes is a common method to understand drug action (Palchaudhuri and Hergenrother, 2010). Changes in gene expression have been studied after treatment with simvastatin, minocycline or progesterone (Anderson et al., 2013; Crack et al., 2009; Vonder Haar et al., 2014). The drugs were tested in the same TBI model allowing a meaningful comparison of their anti-inflammatory action at the level of gene expression (Anderson et al., 2013; Vonder Haar et al., 2014). A caveat of these studies is that the drugs were dosed at a time when the therapeutic effect was unknown (progesterone) or their therapeutic effect was greatly limited when compared to dosing soon after injury (minocycline and simvastatin). Most importantly, these drugs altered expression of many genes thought to mediate inflammatory response. This suggests that these drugs retained anti-inflammatory action when dosed at times when they retained limited potency.

Studies of the anti-inflammatory action of drugs should reflect the changing world of neuroinflammation. For example, many drugs that inhibit microglial activation are interpreted to have an anti-inflammatory effect. Microglia are now known to utilize activation pathways that are broadly termed M1 and M2 (Hanisch, 2013). M1 microglia are considered pro-inflammatory since they produce pro-inflammatory cytokines, chemokines and reactive oxygen species. M2 microglia are anti-inflammatory since they produce anti-inflammatory cytokines, phagocytose cellular debris, and promote tissue remodeling (Hanisch, 2013). This description understates the actual complexity of microglial activation in vivo. Many studies included in this review assessed microglial activation using pan-microglial markers (Iba-1, Cd11b, F4/80) that do not distinguish M1 and M2 cells (Hanisch, 2013) (Tables 2 and 3). Studies that only use pan-microglial markers cannot conclude whether a drug has an anti-inflammatory or pro-inflammatory effect on microglia. Other studies measure inflammatory mediators specific for M1 (iNOS) or M2 (IL-10) without discussing the how the drug modulated microglial activation.

What is the future of preclinical testing of anti-inflammatory drugs to treat TBI? There is presently a lively debate about the utility of mouse or rat models to model human inflammation. This debate centers upon comparison of inflammatory response using gene

expression analysis between mouse and human TBI. Analysis of the same gene expression data resulted in one set of investigators arguing for the utility of rodent animal models while others dismissed the value of animal models (Seok et al., 2013; Takao and Miyakawa, 2014). Limiting or eliminating animal models is not an option for testing drugs for TBI. A clear area of improvement, however, is better design of preclinical testing of drugs to increase the probability for drugs to be effective in clinical trials. The TBI research community should avoid the prior experiences of researchers seeking drug therapies for stroke (Loane et al., 2015). After multiple large clinical trials failed, stroke researchers developed Stroke Therapy Academic Industry Roundtable preclinical recommendations (Fisher et al., 2009). These recommendations can be easily modified to TBI research. When applied to TBI, these recommendations could be: (1) Drugs should improve functional outcomes in multiple experimental TBI models, (2) Dose-response curves should be determined, (3) Drug should have therapeutic windows sufficiently large to permit enrollment of large numbers of patients in a clinical trial. (4) Drugs should be effective in studies that are blinded, physiologically controlled and reproducible. (5) Drugs should produce long-lasting improvements in histological and functional outcomes. (6) Drugs should show efficacy using biomarkers that can be used in humans as well as rodents. (7) Drugs should show efficacy in TBI models using rodents and gyrencephalic species (modified from (Fisher et al., 2009)). Even though some drugs satisfy one or more of these criteria, no one anti-inflammatory drug satisfies all these criteria (Table 2 and 3). These criteria greatly increase the time and expense of preclinical testing; yet preclinical testing remains more rapid and less expensive than clinical trials.

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Table 1

Abbreviations used in this study.

Ad	Adhesive removal test
APA	Active place avoidance
BBB	Blood brain barrier
Cort N	Cortical neuronal loss
CCI	Controlled cortical impact
CD68	Cluster of differentiation protein 68
CHI	Closed head injury
COX-2	Cycloxygenase 2
E + M	Elevated plus maze
FPI	Fluid percussion injury
GFAP	Glial fibrillary acidic protein
Hippo N	Hippocampal neuronal loss
Hippo Ng	Hippocampal neurogenesis
ICAM-1	Intercellular adhesion molecule 1
IL-1β	Interleukin 1 beta
IL-4	Interleukin 4
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-12	Interleukin 12
IL-18	Interleukin 18
Iba-1	Ionized calcium-binding adapter molecule 1
LS	Lesion size
M	Mouse
MAP-2	Microtubule associated protein-2
MMP-2	Metaloprotease 2
MMP-9	Metaloprotease 9
MWM	Morris water maze
M-WD	Marmarou weight drop
NF-κB	Nuclear factor kappa beta
NA	Not applicable
NORT	Novel object recognition
NSS	Neurological severity score
OF	Open field
R	Rat
ROTA	Rotarod
PMN	Polymorphic neutrophils
TBI	Traumatic brain injury
TGFβ	Transforming growth factor beta
TNFα	Tumor necrosis factor alpha
TLR4	Toll-like receptor 4

WD	Weight drop

Table 2

Therapeutic outcomes of drugs with known anti-inflammatory action. The species and TBI model used in each drug study are indicated. The time after injury when inflammatory, histological, molecular or functional outcomes were measured is also indicated.

Outcomes							
Drug	**Species**	**Model**	**Time to first dose**	**Inflammatory**	**Histology or molecular**	**Function**	**References**
Dexamethasone	R	WD	5 min	⇓ Microglia (endothelial-monocyte activating polypeptide II, P2X4 receptor, Iba-1,1,3D), ⇔ (4,6D)			Zhang et al. (2007)
	R	WD	5 min	⇓ Microglia (CD68, MHC II) (5D)	⇓ Edema (5D)		Holmin and Mathiesen (1996)
	R	WD	5 min	⇓ IL-16 (1,2 D), ⇔ (4D), microglia (CD68)			Zhang et al. (2008)
	R	WD	4H	⇔ iNOS (1D)	⇓ Cort N then ⇑ (5,14D)		Gahm et al. (2005)
Indomethacin	R	M-WD	Preinjury	⇓ Il-1β	⇓ Edema		Chao et al. (2012)
	M	WD	10 min	⇓ 6-Keto PGF1α (6 h)	⇔ Edema (6, 24H)	⇔ NSS (6, 24H)	Girgis et al. (2013)
Ibuprofen	M	FP	5 min	⇔ IL-4 (6H, 24H), ⇔ IL-10 (6H, 24H), ⇔ TNFα (6H, 24H), ⇔ Il-1α (6H, 24H), ⇔ IL-6 (6H, 24H)		⇔ NSS (24H), ⇔ ROTA (1D)	Harrison et al. (2014)
Ibuprofin-Vitamin E	M	CCI	5 min			⇑ OF (1D), ⇔ ROTA (1D), ⇔ Barnes maze (1–2D)	Clond et al. (2013)
Roficoxib	R	FPI	5 min		⇓ Hippo N (12–72H)		Kunz et al. (2006)
Nimesulide	M	WD	10 min	⇓ 6-Keto PGF1a (6 h)	⇔ Edema (6, 24 h)	⇔ NSS (6 h and 24H)	Clond et al. (2013)
Celecoxib	R	WD	Preinjury	⇓ Il-1β, ⇔ IL-10 (1D)			Girgis et al. (2013)
Carpofen	M	WD	5 min	⇓ Microglia (Iba-1), ⇓ Il-1 β (4H), ⇓ IL-6 (4H) ⇔ IL-4 (4H), ⇔ IL-10 (4H)	⇓ LS (90D), ⇓ edema (1D), ⇑ ⇑ Gliogenesis (90D)	⇓ NSS (24 h)	Thau-Zuchman et al. (2012)
Meloxicam	M	WD	10 min	⇓ 6-Keto PGF1a (6 h)	⇔ Edema (6, 24 h)	⇔ NSS (6, 24H)	Girgis et al. (2013)
Meloxicam	R	M-WD	30 min	⇓ Lipid peroxidation (2D), GSSH (2D), NaKATPase (48H)	⇓ Edema (24,48H) ⇓ BBB (48H)	⇓ NSS (48H)	Hakan et al. (2010)

Outcomes							
Drug	**Species**	**Model**	**Time to first dose**	**Inflammatory**	**Histology or molecular**	**Function**	**References**
HU-211	R	WD	5 min		⇓ BBB (4H)	⇑ BW (2D), ⇑ balance beam (2D)	Shohami et al. (1993)
HU-211	R	WD	2H		⇓ BBB (4H)	⇑ BW (2D), ⇓ balance beam (2D)	Shohami et al. (1993)
HU-211	R	WD	1,4 or 6H		⇓ Edema (24H)	⇓ NSS (1–30D), ⇓ MWM (1–184)	Shohami et al. (1995)
HU-211	R	WD	5 min	⇓ TNFα (4H)	⇓ Edema (24H), ⇓ BBB (4H), ⇓ Hippo N (14D)	⇓ NSS (1–24H)	Shohami et al. (1997)
Etanercept	R	FPI	5 min	⇓ TNFα, ⇓ Il-1β, ⇓IL-6 (3D)	⇔ LS (4D), ⇓ Cort N (4D), ⇓ astrocyte loss (4D)	⇑ Inclined plane (1–3D)	Chio et al. (2013)
Etanercept	R	FPI	5 min	⇓ TNFα (7D)	⇔ LS (7D), ⇑ Hippo Ng (7D)	⇑ Inclined plane (7D), ⇓ NSS (7D)	Cheong et al. (2013)
3,6'-Dithiothalidomide	M	WD	Preinjury	⇓ TNFα (1–18 h)		⇑Y-maze, ⇑NORT, ⇑Passive avoidance (3, 7D)	Baratz et al.(2011)
Recombinant IL-1 RA	M	Cryogenic	5 min		⇓ LS (1D, 3D), ⇔ edema (1D)	⇑ Balance beam (2H) ⇔ (4–72H), ⇑foot fall (1D)	Jones et al. (2005)
Recombinant IL-1 RA	R	FPI	15 min	⇑ Il-1β (1–72H)		⇓ NSS, ⇑ inclined plane (1, 7,14D)	Knoblach and Faden (2000)
IL-1 RA	R	FPI	15 min		⇓ Cort N (8D), ⇓ Hippo N (8D)	⇓ NSS (7D)	Sanderson et al. (1999)
Anakinra	R	CCI	2H	⇓ iNOS (3D)	LS ⇔ (30D)	⇑ Foot fall (1–10D), ⇔ ROTA (8–12D), ⇔ MWM (14–18D)	Anderson et al. (2013)
Rolipram	R	FPI	Preinjury	⇓ Il-1β (3H), ⇓ TNFα (3H)	⇓ LS (3D), ⇑ CortN (3D), Hippo N ⇑ (3D),⇓ APP (3D),		Atkins et al. (2007)
Rolipram	M	CCI	30 min		⇑ LS (3D)		Atkins et al. (2013)
Rolipram	R	FPI	30 min	⇓ Il-1β (3H), ⇓ TNFα (3H)	⇔ LS (3D), ⇑ BBB		Atkins et al. (2012)
Colchicine	R	WD	5 min	⇓ iNOS (1D),⇓ microglia (CD68, MHC II) (5D)	⇓ Edema (5D),⇓ Cort N (1D)		Holmin and Mathiesen (1996)
Dexamethasone/melatonin	M	CCI	IH	⇓ MMP-2 (1D), ⇓ MMP-9 (1D), ⇓ iNOS (1D)	⇓ LS (1D), ⇓ BAX (1D)	⇑ ROTA (1D)	Campolo et al. (2013)
Etazolate	M	WD	2H	⇓ Il-1β (6,24H), ⇓ microglia (CD11b)	⇓ LSα, ⇓ edema (6,24H), ⇓ sAPPα (1D), ⇓ olefactory bulb	⇓ OF (6, 24H), ⇓ NSS (6, 24H), ⇓ NORT (35D)	Siopi et al. (2011)

Outcomes							
Drug	**Species**	**Model**	**Time to first dose**	**Inflammatory**	**Histology or molecular**	**Function**	**References**
Lipoxin A4	M	WD	10 min	⇓ Il-1β (6, 24H), ⇓ IL-6 (6, 24H), ⇓ TNFα (6, 24H), ⇓ GFAP (1D), microglia (CD11b, 1D)	⇑ LS		Luo et al. (2013)
MK-886	R	FPI	15 min	⇓ LTC4 (1.5H)	⇓ Edema (3D), ⇓ BBB (6H),	⇑ LTP (4D), ⇑ radial arm maze (4–5D)	Corser-Jensen et al. (2014)
NNZ-2566	R	Penetrating	30 min	⇓ Activating transcription factor-3 (1D)			Cartagena et al. (2013)
N-acetyl cysteine	R	WD	15 min	⇓ NF-κB (3D), ⇓ Il-1β (3D), TNFα (3D), ⇔ IL-6 (3D)	⇓ Edema (3D), ⇓ BBB (3D), ⇓ CortN (3D)		Chen et al. (2008)
N-acetyl cysteine	R	CCI	1H		Microglia (Iba-1) 2D	⇔ APA (7D)	Haber et al. (2013)
Resatorvid	M	WD	30 min	⇓ Il-1β, ⇓ TNFα (1D)	⇓ CortN (1D, 7D)		Zhang et al. (2014)
Resatorvid	M	WD	4H			⇓ NSS (1–7D)	Zhang et al. (2014)
TSG-6	M	CCI	6H	⇓ PMN (1D), ⇓ MMP-9 (1D)	⇓ BBB (1D),⇓ LS (14D), Hippo N(70D), Hippo Ng (70D)	⇑MWM (42D), ⇑ Y maze (58D), ⇑ forced swim test (65D)	Watanabe et al. (2013)
VU0360172	M	CCI	3H	⇓ Microglia (NOX2, CD68, 28D), ⇓ NOS (28D), ⇑ Arg-1 (28D)	⇓ LS (28D), ⇓ Hippo N (28D)	⇑ BW (28D)	Loane et al. (2014)

Abbreviations: ⇑, increased outcome measure; ⇓, decreased outcome measure; ⇨, no change in the outcome measure.

Table 3

Therapeutic outcomes of drugs with unknown anti-inflammatory action. The species and TBI model used in each drug study are indicated. The time after injury is also indicated when inflammatory, histological, molecular orfunctional outcomes were measured.

Outcomes							
Drug	**Species**	**Model**	**Time to 1st dose**	**Inflammatory**	**Histological or molecular**	**Functional**	**References**
Minocycline	M	CCI	Preinjury	⇓ Il-1β (4H)	⇓ LS (4D), ⇓ caspase 1 (1D), ⇓ caspase 3 (1D)	⇑ ROTA (1–4D)	Sanchez Mejia et al. (2001)
	M	WD	5 min	⇓ Il-1β (6H), ⇓ MMP-9 (6H)	⇓ Edema (6H), ⇨ glutathione (6H)	⇑ String test (1D)	Homsi et al. (2009)
	M	WD	5 min	⇓ Microglia (1D, CD11b)	⇓ LS(1D), ⇓ βAPP (1D)	⇑ OF (2–84D)	Homsi et al. (2010)
	M	WD	5 min	⇨ Microglia ([^{3}H]-PK11195), (7–9D)	⇨ LS (14D)	⇨ MWM (5–10D)	Kelso et al. (2011)
	M	WD	5 min	⇓ Microglia (CD11b, 90D), ⇓ GFAP (90D)	⇓ LS (90D), ⇓ APPα (1D)		Siopi et al. (2011)
	R	CCI	5 min				
	M	WD	30 min	⇓ Microglia (7D, F4/80)	⇨ Hippo Ng(7D,42D)	⇑NSS (1–7D) then ⇨ (7–42D)	Ng et al. (2012)
	M	CCI	30 min		⇓ LS (4D)	⇑ ROTA (1–4D)	Sanchez Mejia et al. (2001)
	M	CCI	30 min	⇓ Microglia (CD11b/ TNFα, Iba-1/ CD45 2D), ⇓ leukocytes (2D)	⇓ LS (14D), ⇓ body weight (2–14D), ⇓ Hippo N (14D)	⇑ MWM (14D)	Adembri et al. (2014)
	M	WD	30 min	⇓ Microglia (F4/80,4D), ⇨ PMN (1–4D), ⇓ IL-1β (4H), ⇨ IL-1α (4H), ⇨ IL-5 (4H), ⇨ IL-6 (4H), ⇨ IL-10 (4H), ⇨ IL-12 (4H), ⇨ TNFα (4H), ⇨ granulocyte-colony stimulating factor (4H), ⇨ CCL2 (4H), ⇨ CCL3 (4H), ⇨ CXCL2 (4H), ⇨ CXCL3 (4H)	⇓ LS (1D then ⇨ 4D), ⇨ Cort N (1,4D)	⇨ NSS (1–4D)	Bye et al. (2007)
	M	WD	30 min	Changes in gene expression (2–24H)			Crack et al. (2009)

Outcomes							
Drug	**Species**	**Model**	**Time to 1st dose**	**Inflammatory**	**Histological or molecular**	**Functional**	**References**
	R	CCI	1H	⇓ Il-1β (3H)	⇓ LS, ⇨ (14D), ⇑ myelin content (14D)	⇓ APA (7–8D)	Abdel Baki et al. (2010)
	R	CCI	1H	⇓ Microglia (Iba-1, CD68, 2D), ⇨ GFAP (2–14)		⇓ APA (7–8D)	Haber et al. (2013)
	R	CCI	2H	Changes in gene expression (1,3, and 7D)	⇓ LS (25D)	⇨ ROTA (7–11D), ⇑ foot fault (7–16D), ⇨ MWM, (7–11D)	Vonder Haar et al. (2014)
Minocycline plus melatonin	R	CCI	5 min	⇨ Microglia ([^{3}H]-PK11195), (7–9D)	⇨ LS (14D)	⇔ MWM (5–10D)	Kelso et al. (2011)
Minocycline plus N-acetylcysteine	R	CCI	1H	⇓ Il-1β (3H)	⇨ LS (14D), white matter (14D)	⇑ APA (7–8D)	Abdel Baki et al. (2010)
	R	CCI	1H	⇓ Microglia (Iba-1, CD68, 2D), GFAP ⇨ (2–14)		⇑ APA (7–8D)	Haber et al. (2013)
Progesterone	R	WD	30 min	⇓ Il-1β (6H, then ⇨ 24H); ⇓ IL-6 (6H) ⇨ (24H); ⇨TGF (6 and 24H), TNFα (6H) ⇨ (24H): ⇓TGFβ (1D)			Khaksari et al. (2011)
	R	WD	1H	⇓ Cox-2 (1D)	⇓ Caspase 3 (1D)	⇑ MWM (9D)	Si et al. (2013)
	M	CCI	1H	⇓ Il-1R1 (1D), ⇓ Il-6(1D), ⇓ TNFα (1D), ⇓ CxCL10 (1D), ⇓ TLR2 (1D), ⇓ TLR9 (1D), ⇓ CCL2 (1D)			Hua et al. (2011)
	R	CCI	1H	⇓ NF-κB (7D)	⇓ Caspase 3 (3D)	⇑ E + M (4, 24D)	Cutler et al. (2005)
	R	CCI	1H	⇓ Il-6 (1–3D), ⇓ COX-2 (1–3D), ⇓ NF-κB (1–3D)	Caspase 3 (1D), edema (2D)	⇑ OF (72H)	Cutler et al. (2007)
	R	WD	1H	COX-2 (1D), ⇓ PGE2 (1D), ⇓ NF-κB (24H)		⇑ NSS (1D)	Si et al. (2014)
	R	CCI	1H	⇓ NF-κB (2D), ⇓ GFAP (2D)			Pettus et al. (2005)
	R	CCI	1H	⇓ Il-1β (4H) ⇓ TNFα (12H)			He et al. (2004)
	R	CCI	1H	⇓ GFAP (1D)	⇨ LS (19D), ⇓ caspase 3 (1D), ⇓ Bax (1D), ⇑ Cort N(1D)	⇑ MWM* (19–24D)	Djebaili et al. (2005)

Outcomes							
Drug	**Species**	**Model**	**Time to 1st dose**	**Inflammatory**	**Histological or molecular**	**Functional**	**References**
	R	CCI	1H		⇨ LS (19D), Fluoro-Jade (22D), GFAP, MAP-2 ⇨ (22D)	⇨ OF (3D), ⇑Ad (3D, then ⇨), ⇑ MWM (18D)	Tang et al. (2013)
	R	CCI	4H	Changes in gene expression (4H)			Anderson et al. (2011)
Erythropoietin	R	WD	5 min	⇓ Il-6 (1–3D)			Bian et al. (2010)
	R	FPI	5 min	⇓ Il-1β (8H-1D), ⇓ CXCL2 (12, 24H)			Lieutaud et al. (2008)
	R	WD	5 min	⇓ CCL-2 (12H, 2D, 5D), microglia (CD-68,12H, 2D, 5D)	⇓ Cort N (12H, 2D, 5D), ⇓ edema (12H, 2D, 5D)		Xu et al. (2012)
	R	CC	1H	⇓ NF-κB (3D), ⇓ ICAM-1 (3D), ⇓ Il-1β (3D), ⇓ TNFα (3D), ⇨ IL-6 (3D)	⇓ CortN (3D), ⇓ BBB (3D), ⇨ edema (3D)		Chen et al. (2007a)
	M	WD	1H	⇓ C3, ⇓ GFAP (7D)	⇓ Cort N (1D), ⇓ axonal injury (7D)	⇓ NSS, (1H-14D), ⇑ NORT (3D then ⇨ 8D)	Yatsiv et al. (2005)
	R	WD +	1H	⇑ Microglia (CD68, ⇨ 7,14D),	⇓ Hippo N (1D then ⇨ 7,14D),	⇨ ROTA (1–14D), ⇨	Hellewell et al. (2013)
		Hypoxia		⇓ IL-1 (2H)	callosal Axons ⇨ (1–14D), brain stem axons ⇑ (1D then ⇨7, 14D)	NORT (6D), ⇑ OF (6D)	
	R	CCI	1D		⇓ LS (35D), Hippo N (35D), Hippo Ng (35D)	⇑ NSS (1–35D), ⇓ foot fault (1–35D), ⇑ MWM, 31–35D	Meng et al. (2011)
Simvastatin	M	CHI	Pre-injury		⇓ Hippo N (1D)	⇓ ROTA (5D)	Wang et al. (2007)
	R	CCI	1H	⇓ TLR4(1D), ⇓ NF-κB(1D), ⇓ IL-1β (1D), ⇓ IL-6 (1D), ⇓ TNF-α (1D), ⇓ ICAM-1 (1D)	⇓ CortN (1D)	⇓ rota(1D)	Chen et al. (2009)
	R	FPI	1H	⇓ ICAM (1D), ⇓ PMN (1D) ⇨ MMP-9	⇓ BBB (1D), ⇓ edema (1D)	⇓ NSS (6H)	Beziaud et al. (2011)
	R	CCI	2H	Changes in gene expression (1, 3, 7D)	LS ⇨ (25D)	⇨ ROTA (7–11D), ⇑foot fault (7–16D), ⇔ MWM, (7–11D)	Vonder Haar et al. (2014)
	R	CCI	1D	⇓ Il-1β, ⇓ TNFα, ⇓ Il-6 (3D) microglia (CD68, 3D), ⇓ GFAP (3D)		⇨ NSS (1–35D)	Li et al. (2009)
Atorvastatin	M	CHI	Pre-injury		⇓ Hippo N (1D)	⇓ ROTA (5D)	Wang et al. (2007)

Outcomes							
Drug	**Species**	**Model**	**Time to 1st dose**	**Inflammatory**	**Histological or molecular**	**Functional**	**References**
	M	CHI	30 min	⇓ Microglia (CD11b, 1–7D), ⇓ IL-6 (2H-3D), ⇓ TNFα (2H-3D), ⇓ eNOS (2H-3D)	⇓ Hippo N (7D)	⇓ ROTA (5D), ⇑ MWM (24D)	Wang et al. (2007)
Lovastatin	R	CCI	Pre-injury	⇓ Il-1β (6H, 4D), ⇓ TNFα (6H, 4D), ⇓ Il-6 (6H, 4D)	⇓ LS (4D), ⇓ Cort N (4D)	⇓ ROTA (1–7D then ⇨ 14D), ⇑ Ad (1,4D then ⇨ 7,14D)	Chen et al. (2007b)
N-acetyl cysteine	R	WD	15 min	⇓ NF-κB (3D), ⇓ Il-1β (3D), ⇓ TNFα (3D), ⇨ IL-6 (3D)	⇓ Edema, ⇓ BBB, ⇓ Cort N (3D)		Chen et al. (2008)
N-acetyl cysteine	R	CCI	1H	⇨ Microglia (Iba-1, CD68,2D)		⇨ APA (7–8D)	Haber et al. (2013)
Alpha MSH	M	CCI	30 min	⇓ TNFα (1D), ⇓ Il-1β (1D), ⇨ microglia (Iba-1, 1D)	⇓ LS (1D), ⇓ Hippo N(1D)	⇓ NSS (1D)	Schaibleet al. (2013)
COG141Û	M	CCI	30 min	⇓ Microglia (Iba-1, 1, 3, 7D)	⇓APP (3, 7D), corpus callosum and internal capsule volume, IC ⇨ (1,3, 7D), ⇨axonal damage (1,3, 7D)		Byrnes et al. (2012)
Ethyl pyruvate	R	WD	5 min	⇓ TLR4 (1D), ⇓ NF-κB (1D), ⇓ TNFα (1D), ⇓ Il-1β (1D), ⇓ IL-6 (1D)	⇓ Edema (1D)	⇑ BW(1D)	Su et al. (2011)
Oxymatrine	R	WD	5 min	⇓ TLR4 (6H-5D), NF-κB (6H-5D), TNFα (6H-5D), Il-1β (6H-5D), IL-6 (6H-5D),	⇓ Cort N (6H-5D)		Dong et al. (2011)
Palitoylethanolamide	M	CCI	1H	⇓ GFAP (6H-5D), ⇓ microglia (CD11b, 6H-5D), ⇓ NF-κB (1D), ⇓ iNOS (1D), mast cells (1D)	⇓LS (1D), ⇓ edema (1D), ⇓ Cort N (6H-5D), ⇓BAX (1D)	⇑ ROTA (1D), ⇑ swing (1D), ⇑ E + M (2–10D)	Ahmad et al. (2012)
Resveratrol	R	CCI	5 min		⇓ Hippo N(21D), ⇓ LS (21D)	⇑ Beam balance (1–5D), ⇑ BW(5D), ⇑ MWM (18D)	Singleton et al. (2010)
	M	CHI	5 min	⇓ Microglia (Iba-1,3D), ⇓ IL-6 (3D), ⇓ IL-12 (3D)			Gatson et al. (2013)
T3	M	CCI	1H	⇓ Mast cells (1D), ⇓ GFAP (1D), ⇓ iNOS	⇓ LS (1D), ⇓ edema, (1D), ⇓ BAX (1D), ⇑ BCL-2 (1D)	⇓ ROTA (1D), swing (1D), ⇑ E + M (1–10D)	Crupi et al. (2013)

Outcomes							
Drug	**Species**	**Model**	**Time to 1st dose**	**Inflammatory**	**Histological or molecular**	**Functional**	**References**
				(1D), ⇓ NF-κB (1D)			
Triptolide	R	CCI	5 min	⇓ TNFα (1D), ⇓ Il-1β (1D), ⇓ IL-6 (1D), ⇑ IL-10 (1D), ⇓ PGI2 (1D), ⇓ PGE2 (1D)	⇓ LS (1,3D), ⇓ Edema (1, 3D), ⇓ CortN (1, 3D)	⇓ NSS (1–28D), ⇑ ROTA (1–28D), Ad (1–28D), ⇑ BW (1–28D)	Leeet al. (2012)
Wogonin	M	CCI	10 min	⇓ PMN (1D), ⇓ microglia (1D, Iba-1), ⇓ TLR4 (1D), ⇓ NF-κB (1D), ⇓ Il-1β (1D), ⇓ IL-6 (1D), ⇓ CxCL2 (1D), ⇓ COX-2 (1D)	⇓ LS (1,28D), ⇓ edema (1D), ⇓ BBB (1D), ⇓ CortN (1D)	⇓NSS (1–28D), ⇑ BW (1–28D), ⇑ ROTA (1–28D)	Chen et al. (2012)

Abbreviations: ⇑, increased outcome measure; ⇓, decreased outcome measure; ⇨, no change in the outcome measure. The MWM outcome in the Djebaili et al. (2005) study is indicated with an asterisk since the strategy of the mice improved without lowering the time to find the hidden platform.