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REVIEW

Preclinical Studies on Mechanisms Underlying the Protective Effects of Propranolol in Traumatic Brain Injury: A Systematic Review

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Abstract
Traumatic brain injury (TBI) is a leading cause of mortality and morbidity amongst trauma patients. Its treatment is focused on minimizing progression to secondary injury. Administration of propranolol for TBI maydecrease mortality and improve functional outcomes. However, it is our sense that its use has not been universally adopted due to low certainty evidence. The literature was reviewed to explore the mechanism of propranolol as a therapeutic intervention in TBI to guide future clinical investigations. Medline, Embase, and Scopus were searched for studies that investigated the effect of propranolol on TBI in animal models from inception until June 6, 2023. All routes of administration for propranolol were included and the following outcomes were evaluated: cognitive functions, physiological and immunological responses. Screening and data extraction were done independently and in duplicate. The risk of bias for each individual study was assessed using the SYCLE's risk of bias tool for animal studies. Three hundred twenty-three citations were identified and 14 studies met our eligibility criteria. The data suggests that propranolol may improve post-TBI cognitive and motor function by increasing cerebral perfusion, reducing neural injury, cell death, leukocyte mobilization and p-tau accumulation in animal models. Propranolol may also attenuate TBI-induced immunodeficiency and provide cardioprotective effects by mitigating damage to the myocardium caused by oxidative stress. This systematic review demonstrates that propranolol may be therapeutic in TBI by improving cognitive and motor function while regulating T lymphocyte response and levels of myocardial reactive oxygen species. Oral or intravenous injection of propranolol following TBI is associated with improved cerebral perfusion, reduced neuroinflammation, reduced immunodeficiency, and cardio-neuroprotection in preclinical studies.

Keywords Traumatic brain injury · Propranolol · Beta-blockade · Cognition

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality among trauma patients (Waxweiler et al. 1995) and results in heavy societal socioeconomic burdens (Maas et al. 2017). Survivors often experience long-term disability, loss of functional independence, poor quality of life and loss of productivity in addition to deficits in cognition, memory, mobility, and psychosocial function (Ma et al. 2014).

Pathophysiology

TBI is a complex biphasic pathophysiological condition characterized by primary and secondary injuries. Primary injury is caused by direct mechanical insult to brain tissue. Secondary injury occurs as a result of a cascade of events leading to neuronal cell death following the injury (Lerouet et al. 2021). During the period of secondary injury there is a catecholamine surge (Rizoli et al. 2017), which causes hyperthermia, hypertension, tachycardia, tachypnea, and diaphoresis. The adrenergic storm induced by the initial insult may worsen the prognosis by cerebral vasoconstriction induced ischemia (MacKenzie et al. 1976).

Excitotoxicity involves neurons firing too frequently causing the release of excess s glutamate and results in increased intracellular calcium (Weber 2012). This causes activation of endonucleases, proteases, and phospholipases that damage DNA, cell membranes, and other crucial cellular structures (McGuire et al. 2019). Oxidative stress is another contributor to secondary injury caused by an excess production of reactive oxygen and nitrogen species leading to lipid peroxidation, protein carbonylation and DNA oxidation (Lerouet et al. 2021).

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Neuroinflammation is also a key factor in the exacerbation of secondary injury. Inflammatory responses involve recruitment of peripheral monocytes, neutrophils, and lymphocytes through the blood-brain barrier by resident immune cells (Simon et al. 2017). Upon activation, glial cells can release proinflammatory cytokines such as TNF, IL-6, and IL-1β.

Role of Beta Blockade

Little progress has been made towards improving the treatment of TBIs. Existing treatment paradigms focus on minimizing progression of secondary injury (Ma et al. 2014) by maintaining adequate brain perfusion, limiting cerebral edema, and optimizing oxygen delivery (Kochanek et al. 2019). Increased catecholamine levels drive the systemic inflammatory response (Di Battista et al. 2016a), coagulopathy, and endotheliopathy (Di Battista et al. 2016b); increase cardiac and cerebral oxygen demands (Dünser and Hasibeder 2009); lead to hypermetabolism and loss of lean body mass (Monk et al. 1996); and cause vasogenic cerebral edema by increasing intracapillary hydrostatic pressure edema (Naredi et al. 1998; Chioléro et al. 1989; Friese et al. 2008). Because excessive catecholamine release is a major catalyst in augmenting secondary injury, reducing this response is an area of potential therapeutic interest (Sasaki and Dunn 2001). Several large retrospective cohort studies in TBI patients receiving beta-blockers reported improved neurologic outcomes (Heffernan et al. 2010; Cotton et al. 2007; Arbabi et al. 2007; Inaba et al. 2008). Based on a recent systematic review (12,721 patients in 15 human studies), the administration of propranolol in patients with TBI significantly improved survival and was associated with improved long-term functional outcome when compared to patients who did not receive treatment (Ding et al. 2021). Furthermore, propranolol did not increase the series of serious adverse events. By counteracting the catecholamine surge following TBI, beta-adrenergic receptor blockade may reduce the cascade of secondary injuries and improve neurological outcomes (Rizoli et al. 2017).

Murine models have shown that early beta-blocker administration increases cerebral perfusion, decreases cerebral hypoxia and edema, and improves neurologic recovery (Ley et al. 2010). Propranolol, a lipophilic agent, is considered the beta-blocker of choice because it readily penetrates the blood-brain barrier (Neil-Dwyer et al. 1981). Catecholamine inhibition may reduce cerebral vasospasm and improve delivery of cerebral oxygen (Schroeppel et al. 2014). Other plausible mechanisms include decreased cerebral oxygen consumption and reduced immunodeficiency (Ley et al. 2010). For example, a reduction in metabolic rate with propranolol administration, thereby reducing energy expenditure and protein catabolism in patients with TBI has been reported (Chioléro et al. 1989). Another study of 55 trauma patients in the ICU treated with beta-blockers reported that beta blockade reduced circulating levels of IL-6 in trauma patients (Friese et al. 2008). Given its potential to reduce secondary injury after TBI, propranolol has been introduced as an early-response treatment in some hospitals. Likely due to low certainty of evidence evaluating efficacy with beta blockers in TBI and the potential for adverse effects (e.g. bradycardia and hypotension), their use in this population has not been universally adopted. An improved understanding of the molecular and physiological mechanisms by which propranolol attenuates secondary injury following TBI will inform future research and improve clinician confidence with the medication in this patient population. The objective of this systematic review of preclinical studies is to explore the mechanism of propranolol as a potential therapeutic intervention in TBI. Ouraim was to summarize succinctly the plausible mechanisms for propranolol's action to inform future clinical trials.

Methods

Medline,Embase and Scopus were searched from inception until June 6, 2023 (Appendix 1 provides the Medline, Embase, and Scopus search strategies). A preliminary literature search was conducted, which showed that majority of the preclinical studies were conducted after the 2000s. Included were all published, full-text, primary studies in English that investigated the effect of propranolol on the management of TBI in animal models. Studies reporting on any models of induced-TBI using any method and in any species were included. Currently, there is insufficient evidence in humans to conduct a systematic review. Animal models are useful before clinical studies can be performed or for generating hypotheses. Furthermore, animal studies were chosen because the study subjects are much more homogenous in their injury patterns and the time between injury and testing, facilitating the interpretation of their responses to treatment. All routes of administration for propranolol (intravenous, intraperitoneal, and oral) were included. Outcomes including changes in cognitive functions as well as physiological or immunological responses were evaluated. Studies were excluded for the following reasons: wrong study design, wrong intervention, wrong patient population and duplicate studies.

Two reviewers (J.J. and Y.L.) independently screened the titles and abstracts of all citations identified with the search. Subsequently, the same reviewers screened full-texts of identified studies. Disagreements were resolved using a third reviewer (I.B.), when necessary. Covidence® (2023) was used to facilitate the screening process. References of

eligible full text articles were screened for additional studies and presented a descriptive synthesis of the results from the included studies.

Data Extraction and Risk of Bias Assessment

Study information including study design, animal model, propranolol administration, outcomes, and major findings were collected independently by two reviewers and organized using Excel (Excel for Mac 2021, version 16.56; Redmond, WA). The same two reviewers who screened the articles independently conducted the risk of bias assessment of the included studies using the SYCLE's risk of bias tool for animal studies (Hooijmans et al. 2014). The domains assessed include selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attribution bias (incomplete outcome data), reporting bias (selective outcome reporting), and other sources of bias.

Results

Of the 323 citations identified in the search, 14 studies met our eligibility criteria (Fig. 1) (Armstead and Vavilala 2019; Genét et al. 2018; Kota et al. 2016; Larson et al. 2012; Ley et al. 2009, 2010, 2012; Lopez et al. 2022a; Lopez et al. 2022b; Singer et al. 2023; Wallen et al. 2022; Yang et al. 2019; Zeeshan et al. 2019; Zlotnik et al. 2012). Studies used different animals including Yorkshire pigs (Armstead and Vavilala 2019), Sprague-Dawley rats (Genét et al. 2018; Kota et al. 2016; Larson et al. 2012; Yang et al. 2019; Zlotnik et al. 2012), C57/Bl6 mice (Ley et al. 2012; Zeeshan et al. 2019; Singer et al. 2023; Wallen et al. 2022), CD1 mice (Lopez

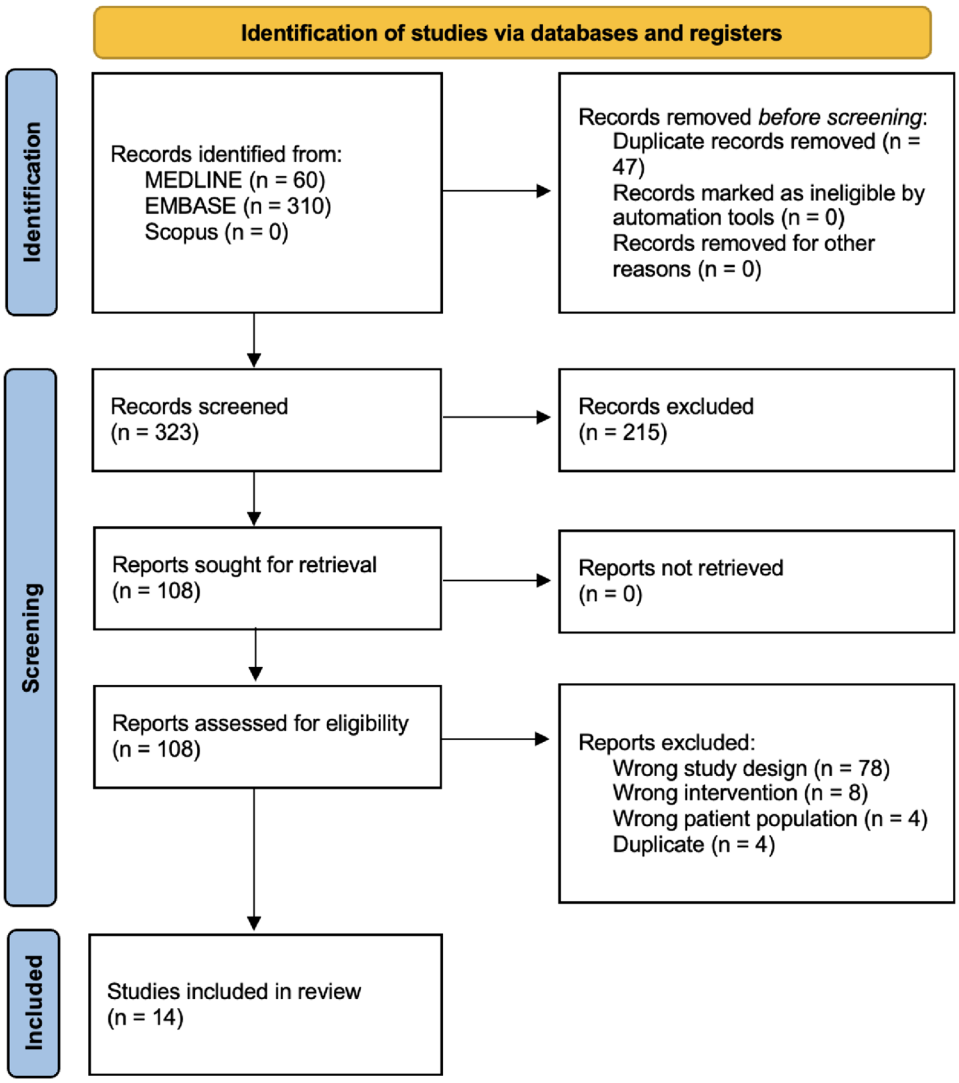

Fig. 1 PRISMA flowchart of systematic review

et al. 2022a, b), and BALB/C mice (Ley et al. 2010; Ley et al. 2009). TBI was induced with either weight-drop (Ley et al. 2010; Ley et al. 2009; Singer et al. 2023; Wallen et al. 2022), controlled cortical impact (Kota et al. 2016; Yang et al. 2019), closed-head injury (Zlotnik et al. 2012; Ley et al. 2012; Zeeshan et al. 2019), or lateral fluid percussion (Armstead and Vavilala 2019; Genét et al. 2018; Larson et al. 2012), (Fig. 2).

Propranolol was administered via different routes including intravenous (Ley et al. 2010; Armstead and Vavilala 2019; Genét et al. 2018; Ley et al. 2012), intraperitoneal (Kota et al. 2016; Yang et al. 2019; Zlotnik et al. 2012; Zeeshan et al. 2019; Lopez et al. 2022a, b; Singer et al. 2023; Wallen et al. 2022; Ley et al. 2009), or oral (Larson et al. 2012). Studies reported physiological, immunologic, and cognitive outcomes. Physiological responses included blood pressure, heart rate (Genét et al. 2018; Larson et al. 2012; Zlotnik et al. 2012), catecholamine levels (Genét et al. 2018; Kota et al. 2016; Yang et al. 2019), glucose metabolism (Ley et al. 2012; Zlotnik et al. 2012), body weight loss (Lopez et al. 2022a, b), blood brain barrier permeability (Genét et al. 2018; Kota et al. 2016; Lopez et al. 2022a, b), cerebral perfusion, and hypoxia (Ley et al. 2010; Larson et al. 2012; Ley et al. 2009). Immunological responses included change in serum or cerebrospinal fluid cytokine levels (Armstead and Vavilala 2019; Ley et al. 2012; Wallen et al. 2022; Zeeshan et al. 2019), and immune cell responses of leukocytes (Lopez et al. 2022a, b), microglia, macrophage (Kota et al. 2016), T-cells, and B-cells (Yang et al. 2019). Cognitive functions were examined using spatial learning, memory, or sensorimotor tests (Kota et al. 2016; Larson et al. 2012; Ley et al. 2012; Zeeshan et al. 2019; Lopez et al. 2022a, b; Singer et al. 2023). Some studies also reported changes in expressions of heat shock protein (HSP70) (Ley et al. 2012; Zeeshan et al. 2019), a prognostic marker for survival in TBI and inhibitor of apoptosis (Ley et al. 2012; Beere et al. 2000); ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL-1) (Zeeshan et al. 2019), a brain-specific marker of injured neurons (Zeeshan et al. 2019; Day and Thompson 2010); and hyperphosphorylated tau (p-tau) (Singer et al. 2023), which has been linked to the development of chronic traumatic encephalopathy, Alzheimer's and Parkinson's disease (Katsumoto et al. 2019; Padmakumar et al. 2022).

The summary of propranolol's proposed mechanisms based on preclinical studies is illustrated in Fig. 3. Data extraction was conducted on all selected studies and study summary was described in Table 1. The risk of bias assessment suggested that the included studies had minimal risk in reporting bias, attribution bias, and other sources of biases (Table 2). However, most studies did not have sufficient information for assessment of selection bias (allocation concealment), performance bias (random housing, blinding), and detection bias (random outcome assessment). Notably, one study randomly assigned mice to experimental groups based on the date of receiving the mice (Singer et al. 2023); another reported the number of rearing and ambulatory events for motor performance but subsequently illustrated the data as a ratio of TBI/sham mice (Ley et al. 2012). Thus, these two studies potentially have a high risk of bias in allocation concealment and selective outcome reporting, respectively.

Types of Preclinical TBI Models

In fluid percussion injury (FPI), fluid pulses are applied directly to exposed dura. This model permits control over dwell time and impact pressure. The controlled cortical impact (CCI) model uses a controlled piston to penetrate the exposed dura. The CCI model allows for control over the depth, speed, and dwell time of the piston in a highly

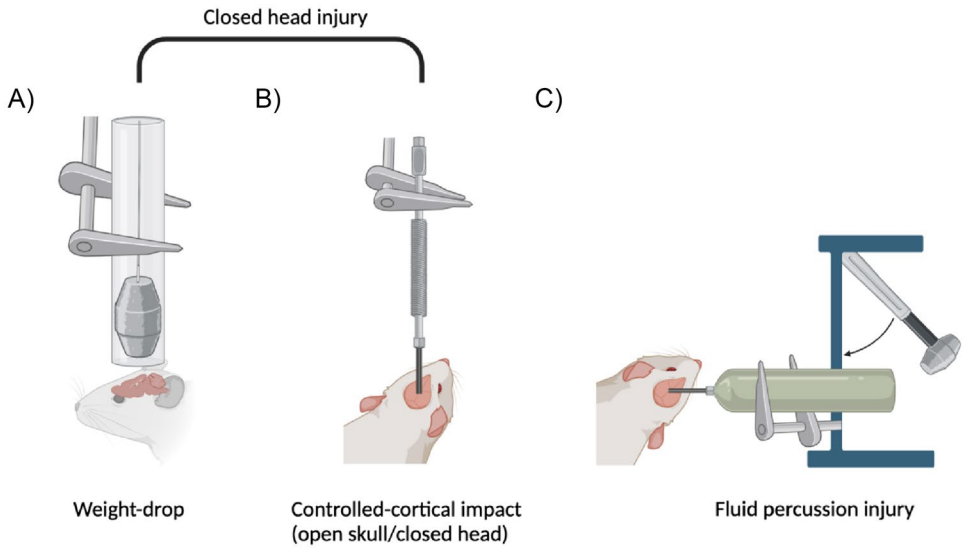

Fig. 2 Illustration of the various traumatic brain injury animal models identified from the preclinical studies including **A**) weight-drop, **B**) controlled cortical impact (CCI), **C**) and fluid percussion injury (FPI)

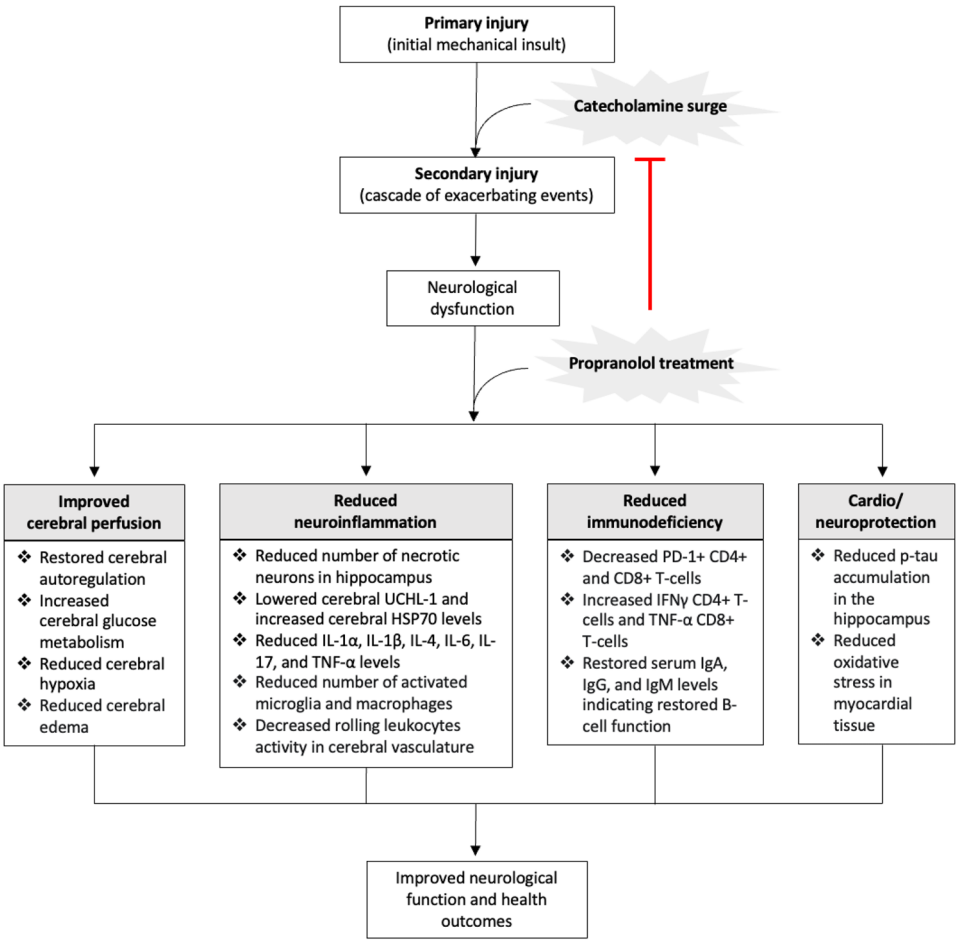

Fig. 3 Summary of the proposed mechanisms of propranolol in traumatic brain injury

reproducible fashion. Because the FPI and CCI models require craniotomy, they change the intracranial pressure, alter the immune response, and result in high mortality in the mice. Alternatively, the weight-drop model involves using a free-falling weight that directly impacts an open or closed skull. It resembles the injury mechanism in human patients with TBI.

Cerebral Perfusion

Several randomized trials by the Ley group have evaluated the effect of propranolol on cerebral perfusion in animal models (Ley et al. 2009, 2010, 2012). In 2009, they measured cerebral perfusion and hypoxia in BALB/C mice that underwent injury via a weight-drop model (Ley et al. 2009). The investigators administered intraperitoneal injections of propranolol (10 mg/kg) 15-minutes and 24-hours post-TBI. Compared to the placebo, mice that received propranolol treatment displayed significant improvements in cerebral perfusion measured by immunohistochemistry and PET imaging. Cerebral hypoxia was reduced by 24.2% compared to placebo. Another study examined the effects of varied dosing and timing of propranolol treatment in BALB/C mice with severe TBI induced by the same weight-drop model (Ley et al. 2010). Injured mice were subject to an intravenous injection of propranolol at high-dose (4 mg/kg) or low-dose (1 mg/kg) at either 15- or 60-minutes following injury. Propranolol treatment at high dose displayed significant improvements in cerebral reperfusion measured by PET standard uptake value (SUV) compared to the placebo in both the early and delayed intervention groups, and low dose propranolol was inferior to high dose in the early intervention groups. This implies that, early, high-dose propranolol treatment may be effective at attenuating TBI-related reduction in cerebral perfusion in animal models. Additionally, the group also measured the cerebral glucose metabolism, motor performance, inflammatory cytokine level/expression, and HSP70 expression (a prognostic marker for survival in TBI) of C57/Bl6 mice that were subjected to controlled cortical impact injury and treated with propranolol (Ley et al. 2012). Previously, TBI patients have shown reduced cerebral glucose metabolism as characterized by increased lactate/pyruvate ratio (Vespa et al. 2005). Propranolol treatment was associated with normalization of cerebral glucose metabolism comparable to that of the uninjured mice (Ley et al. 2012). Moreover, propranolol-treated mice performed significantly better at rotarod and rearing tests 24 hours after injury, indicating improved

Table 1 Summary of animal studies included in the systematic review

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Armstead and Vavilala 2019, USA	Y	Y	Y	newborn Yorkshire pigs w/ gyrencephalic brain; closed cranial window; moderate (2 atm) lateral FPI; intensity of injury (1.9–2.2 atm for 19–23 ms)	intravenous	1 mg/kg at 1 hour after FPI	1	pial artery diameter during hypotension, IL-6 CSF levels, transient hyperaemic response rate, necrotic cell count	Propranolol 1) prevented the impairment of hypotensive dilation (109 ± 14 µm after FPI vs. 136 ± 21 µm after FPI and propranolol), 2) limited TBI-related hyperactive sympathetic activity, 3) restored THRR after both unilateral and bilateral carotid artery compression in both male and female mice ($p = 0.001$), 4) reduced the number of necrotic neurons in cornu amonis (CA1 and CA3) in hippocampus ($p = 0.001$), 5) reduced CSF IL-6 concentration 4 hours after fluid percussion injury ($p = 0.001$)
Genét et al. 2018, Denmark	Y	Y	Y	Sprague-Dawley rats; lateral FPI; 2.4 atm	intravenous (right internal jugular vein)	10 mins post-TBI; bolus dose over 2–3 minutes + infusion for 24 hours of treatment (propranolol group = 5 mg/kg + 1.5 mg/kg/hr. infusion; propranolol/clonidine group = 1 µg/kg clonidine + 1 µg/kg/hr. infusion; propranolol treatment/vehicle group = 0.2 mL/kg 0.9% NaCl + 0.2 mL/kg/hr. infusion)	1	mean arterial pressure, heart rate, syndecan-1, epinephrine, norepinephrine, brain water content, plasma volume, blood chemistry, blood brain barrier permeability, glycocalyx disruption, cell disruption	1) Propranolol or propranolol + clonidine decreased mean arterial pressure and heart rate; Propranolol 2) increased epinephrine levels significantly 2 hours after treatment ($p < 0.05$), 3) but did not alter brain water content and blood brain barrier permeability 24 hours post TBI

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Kota et al. 2016, USA	Y	Y	Y	Sprague-Dawley rats; CCI; a single impact of 3.1-mm depth of deformation with an impact velocity of 5.8 m/s and a dwell time of 150 ms; moderate to severe injury to the parietal cortex	intraperitoneal (propranolol); intravenous (mesenchymal stem cells)	propranolol (10 mg/kg 1 hour post CCI); MSC (10^6 MSC/kg 72 hours post); propranolol + MSC (same doses as previously mentioned)	1	edema, serum norepinephrine, blood brain barrier permeability, macrophage/ microglia distribution and activation, neurogenesis (DCX+ cells), cognitive function	Propranolol 1) decreased edema in the brain ($p<0.05$), 2) decreased the level of serum norepinephrine, 3) lowered the BBB permeability but not significantly, 4) decreased the number of fully activated microglia/macrophage ($p<0.05$); Propranolol + MSCs combined treatment ($p<0.01$) and MSCs alone ($p<0.05$) 5) significantly lowered BBB permeability at 96 hours post TBI, 6) decreased the number of fully activated microglia/macrophage (MSC alone $p<0.01$, or propranolol + MSC combined treatment $p<0.01$); Propranolol + MSC combined treatment 7) decreased the total number of macrophages/ microglia recruited to the injured brain 7 days after injury, 8) increased neurogenesis as indicated by the presence of DCX+ cells on the ipsilateral side of the injury 7 days after injury, 9) restored spatial learning and memory of rats exposed to controlled cortical injury, 10) decreased macrophage/microglia recruitment 150 days after injury, 11) decreased the number of DCX+ cells on the ipsilateral side, indicating less neurogenesis in the long term
Larson et al. 2012, USA	Y	N	Y	adult male Sprague-Dawley rats; controlled FPI	oral	rats took propranolol dissolved in tap water ad libitum for 10 days post TBI; assumed a mean water intake of 35 mL/day and 50 mg/kg/day of propranolol intake per rat	ad libitum	blood pressure, left ventricle contractability, oxidative stress, gliosis, sensorimotor coordination testing, reactive oxygen species (ROS)	1) Propranolol reduced oxidative stress in myocardial tissues by decreasing the level of reactive oxygen species ($p<0.05$); TBI 2) was associated with increased gliosis, 3) significantly decreased sensorimotor coordination 3 days post injury

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Ley et al. 2012, USA	N	N	Y	C57/B16 mice; closed head injury (3 mm depth, 3 m/s, 30 ms dwelling)	intravenous	tail vein injection with a volume of 120 uL of either saline or propranolol (4 mg/kg)	1	cerebral glucose metabolism, motor performance, cerebral cytokine, heat shock protein (HSP70)	Propranolol 1) increased cerebral glucose metabolism, 2) improved motor performance including rotarod test (44 vs. 23 sec, $p<0.01$), ambulatory events (4589 vs. 3729 events, $p=0.33$), and rearing activity (338 vs. 130 events, $p=0.01$) 24 hours after injury, 3) decreased the cerebral expressions of IL-6 and IL-1B 24 hours post TBI
Ley et al. 2010, USA	Y	N	Y	BALB-C mice; weight-drop (38 g weight, @ 30 cm, 1140 g cm injury)	intravenous	tail vein injection with a volume of 120 uL of 1 mg/kg (low dose), 4 mg/kg (high dose) propranolol or saline; propranolol was administered at either 15 minutes or 60 minutes after injury	1	cerebral perfusion, cerebral hypoxia, cerebral edema, neurologic recovery	1) High dose treatment displayed significant improvements in cerebral reperfusion measured by PET standard uptake value (SUV) compared to the placebo in both the early and delayed intervention groups (0.515 ± 0.01 SUV vs 0.395 ± 0.01 SUV at 15 minutes; 0.43 ± 0.02 SUV vs 0.26 ± 0.03 SUV at 60 minutes); 2) Low dose treatment was inferior to high dose in the early intervention groups (0.46 ± 0.01 vs 0.515 ± 0.01, $p<0.01$); 3) Early treatment also showed greater improved cerebral perfusion but unsure if significant
Ley et al. 2009, USA	Y	Y	Y	BALB-C mice; weight-drop (38 g weight, @ 30 cm, 1140 g cm injury)	intraperitoneal	injection of 200 uL of either saline or saline with propranolol (10 mg/kg) at 15 minutes and 24 hours after injury	2	vessel density, vessel perfusion, cerebral hypoxia	Propranolol 1) restored cerebral perfusion measured by immunohistochemistry (152% increase in *Ricinus communis* agglutinin-lectin staining) and PET imaging (130% increase in the copper-pyruvaldehyde-bis(N4-methylthiosemicarbazone) tracer activity), 2) significantly reduced cerebral hypoxia by 24.2% compared to placebo (mean quantitated hypoxic area of 562 ± 20 vs 426 ± 19)

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Lopez et al. 2022b, USA	Y	Y	Y	CD1 adult male mice; CCI (cortical deformation depth of 1 mm, 6 m/s, 3 mm-diameter impactor tip)	Intraperitoneal	injection of saline or propranolol-hydrochloride at 1 mg/kg (low dose), 2 mg/kg or 4 mg/kg (high dose) 1 hour post injury or sham surgery	4	number of rolling leukocytes and blood brain barrier permeability on penumbral endothelium, edema, body weight loss, neurological function (Garcia Neurological Test)	Propranolol 1) significantly decreased leakage in the penumbral blood brain barrier in a dose dependent manner 48 hours after injury compared to the untreated group (untreated, 56.8 ± 1.9%; 1 mg/kg, 49.8 ± 1.2%, $p < 0.001$; 2 mg/kg, 45.2 ± 1.2%, $p < 0.001$; 4 mg/kg, 39.3 ± 1.2%, $p < 0.001$), 2) significantly reduced edema measured by wet-to-dry ratio in the hemisphere ipsilateral to the injury in all groups compared to saline treatment ($p < 0.001$), 3) prevented and reversed body weight loss 24 hours following TBI; High-dose treatment 4) significantly decreased the number of rolling leukocytes on the penumbral endothelium in a dose dependent manner (4 mg/kg, 5.9 ± 0.39 LEUs/100 µm/min vs. saline, 23.6 ± 1.0 LEU/min, $p < 0.001$; 4 mg/kg vs. 1 mg/kg, 13.0 ± 0.45 LEUs/100 µm/min, $p < 0.001$), 5) significantly improved neurological function (GNT scores) 24 hours after injury (2 mg/kg, 15.7 ± 1.6, $p = 0.02$; 4 mg/kg, 16.1 ± 0.1, $p = 0.001$)
Lopez et al. 2022a, USA	Y	Y	Y	CD1 male mice (25–30 g); CCI (cortical deformation depth of 1 mm, 6 m/s, 3 mm-diameter impactor tip)	intraperitoneal	injection of 1 mg/kg, 2 mg/kg or 4 mg/kg (high dose) propranolol 1 hour post injury, twice a day for 14 days to injured animals; injection of saline or 2 mg/kg propranolol to sham surgery animals	28	number of rolling leukocytes and venular permeability in pial microvasculature, body weight loss, neurological function (Garcia Neurological Test)	Propranolol 1) was associated with improved neurological function 14 days post-injury, 2) 2, 4 mg/kg doses significantly reversed body weight loss 14 days post-injury; 3) High dose treatment significantly decreased leukocyte rolling on the pial microvasculature 14 days post-injury (saline, 2.0 ± 0.71 LEUs/100 µm/min vs. 4 mg/kg, 1.0 ± 0.55 LEUs/100 µm/min, $p = 0.03$)

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Singer et al. 2023, USA	Y	Y	Y	C57/BL6 mice (male and female); weight-drop (400 g, @ 2.5 cm, 1000 g cm injury); blood was drawn to reach mean arterial pressure of 25 mmHg and maintained for 60 minutes to induce hemorrhagic shock	intraperitoneal	injection of 4 mg/kg propranolol or saline; propranolol was administered at 90 minutes after injury (20 minutes after hemorrhagic shock)	1	p-tau accumulation, time to raft in the Morrison Water Maze test	1) TBI induced p-tau accumulation; 2) Hemorrhagic shock exacerbated p-tau accumulation ($p=0.007$ for IHC, $p=0.029$ for IF) following TBI but not alone; Propranolol 3) significantly reduced p-tau accumulation in the hippocampus in both mice subjected to TBI alone ($p<0.0001$ for IHC) or TBI complexed with hemorrhagic shock (IHC, $p<0.0001$; IF, $p=0.012$) 30 days after injury, 4) was associated with a significant improvement in the hippocampal-dependent Morrison Water Maze test (reduction in time to raft) in both mice with TBI ($p=0.0164$) and TBI complexed with hemorrhagic shock ($p=0.0013$)
Wallen et al. 2022, USA	Y	Y	Y	C57/BL6 mice (male); weight-drop (400 g, @ 2.5 cm, 1000 g cm injury); blood was drawn to reach mean arterial pressure of 25 mmHg and maintained for 60 minutes to induce hemorrhagic shock	intraperitoneal	injection of 4 mg/kg propranolol, 100 mg/kg TXA or 100 µL saline; propranolol was administered at 90 minutes after injury (30 minutes after hemorrhagic shock) combined with either whole blood resuscitation or hypertonic saline	1	serum IL-2, IL-12, IL-6, MIP-1α, and neuro-specific enolase levels, cerebral IL-1α, IL-1ß, IL-4, IL-17, and TNF- α levels	Propranolol + WB was associated with 1) a significant increase in serum IL-2 & IL-12 levels in TBI/shock mice at 6 and 24 hours post-injury, 2) a significant decrease in serum IL-6 levels in TBI/shock mice at 6 hours post-injury, 3) a significant increase at 1 hour and a significant decrease at 24 hours in serum MIP-1α levels post-injury, 4) a significant decrease in serum NSE levels at 24 h post-injury, 5) a significant decrease in cerebral IL-1α and IL-1ß levels at 6 h post-injury; 6) Propranolol + HTS was associated with a significant decrease in cerebral IL-1α, IL-1ß, IL-4, IL-17, and TNF- α levels at 24 h post-injury

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Yang et al. 2019, China	Y	N	Y	Male Sprague-Dawley rats; controlled cortex injury was made perpendicularly by a pistol rod (3.0 mm diameter for contact surface, 1.5 mm vertical cortical impact depth, 3.0 m/s impact velocity, 100.0 ms contact time)	intraperitoneal	6 mg/mL propranolol hydrochloride dissolved in 0.9% NaCl ➔ at 10 mg/kg immediately before TBI, 4 & 8 h post)	3	frequency of CD4+ and CD8+ T cells, serum IgA, IgG, IgM levels, NE, T cell exhaustion	Propranolol 1) decreased the frequency of PD-1 positive CD4+ (18.5% to 11.7%, $p=0.01$) and CD8+ (13.0% to 8.4%, $p=0.05$) T cells, 2) increased the frequency of IFN-gamma positive CD4+ T cells (6.5% to 11.1%, $p<0.001$) and TNF-alpha positive CD8+ T cells (7.3% to 12.2%, $p=0.001$); 3) Blocking PD-1 increased the frequency of IFN-gamma positive CD4+ (6.1% to 10.8%, $p<0.001$) and TNF-alpha positive CD8+ T cells (6.5% to 11.4%, $p<0.001$); Increase in NE can 4) reduce the frequency of IFN-gamma positive CD4+ T cells and TNF-alpha positive CD8+ T cells; 5) increase the frequency of PD-1 positive CD4+ and CD8+ T cells by Day 2; 6) B cell dysfunction following injury is likely dependent on the presence of PD-1 positive CD4+ T cells as inhibiting PD-1 positive CD4+ T cells significantly restored B cell function as indicated by serum IgA, IgG, and IgM levels
Zeeshan et al. 2019, USA	Y	Y	Y	Male C57/BI6 mice; closed-cortical impact; impact was made on the left frontoparietal area with a velocity of 4 m/s, a deformation depth of 1 mm, and a dwell time of 500 msec	intraperitoneal	injection of propranolol or saline at 4 mg/kg at 2 hours and Day 1 through 6 after injury	7	Memory, learning, cognitive function, inflammation (IL6, IL1B, TNFa)	Propranolol 1) was associated with significantly higher novel object recognition after 2 days (0.524 ± 0.089 vs. 0.465 ± 0.084 NOR ratio, $p=0.03$) and significantly less time to complete the maze after 4 days (19 ± 6.2 vs. 28 ± 10.4 sec, $p=0.03$) compared to the placebo, 2) significantly lowered UCHL-1 ($p=0.03$) & increased HSP70 ($p=0.01$) in the brain

Table 1 (continued)

Author, year, country	Study design (Y/N)			Model	Intervention protocol			Outcomes	Major findings
	Randomization	Blinded	Control group		Route of administration	Treatment modality and duration	Number of treatment sessions		
Zlotnik et al. 2012, Israel	Y	Y	Y	Male Sprague-Dawley rats; closed head injury; a cranial impact of 0.5 J was delivered by a silicone-coated rod 1–2 mm lateral to the midline of the skull	intraperitoneal	propranolol hydrochloride at 10 mg/kg either 60 minutes before or after injury; injection of metoprolol at 10 mg/kg 60 minutes before injury; injection of isoproterenol at 50 µg/kg 30 minutes before injury; injection of butoxamine at 10 mg/kg at 40 minutes before injury and 10 minutes the injection of isoproterenol	1	Blood glutamate, blood glucose, mean arterial blood pressure, heart rate	Propranolol 1) significantly improved the neurological severity score only at 60 minutes after but not at 24 & 48 h post TBI, 2) did not change blood glutamate levels compared to the saline control; 3) Percent decrease in blood glutamate levels 90 minutes after TBI was associated with increased neurological severity score 24 h after TBI ($r^2 = 0.73$)

* *BBB* blood brain barrier, *CCI* controlled cortical impact, *FPI* fluid percussion injury, *HTS* hypertonic saline, *MSC* mesenchymal stromal cells, *NSE* neuro-specific enolase, *TXA* tranexamic acid, *WB* whole blood resuscitation

motor function (Ley et al. 2012). Additionally, HSP70 is an anti-apoptotic protein that can protect neuronal cells from both apoptosis and necrosis by directly inhibiting activators of both mechanisms, and by upregulating the expressions of other anti-apoptotic proteins such as bcl-2 (Giffard and Yenari 2004; Yenari 2005). One study suggested that propranolol treatment was associated with significantly higher levels of HSP70 and lower levels of UCHL-1 in C57BL/6 mice subjected to closed head controlled cortical impacts (Zeeshan et al. 2019). Overall, current literature suggests that propranolol may reduce secondary injury following TBI and improve cognitive and motor functions by increasing cerebral perfusion in animal models.

Cognitive Function

Recent studies have shown a statistically significant association between cerebral IL-6 and propranolol treatment. In a study using a pig model subjected to fluid percussion injury to investigate whether an increase in IL-6 following TBI is associated with impaired cerebral autoregulation and neuronal cell necrosis in the hippocampus, investigators measured changes in artery diameter, number of necrotic neurons, transient hyperaemic response ratio (THRR), and cerebrospinal fluid IL-6 levels (Armstead and Vavilala 2019). Specifically, THRR measured the change in blood flow before and after compression in the common carotid artery. Propranolol treatment was associated with a higher THRR, and an increase in artery diameter during hypotension, indicating restored cerebral autoregulation. Moreover, propranolol treatment 4 hours after injury reduced cerebrospinal fluid IL-6 levels and decreased the number of necrotic neurons in the hippocampus.

Another study measured leukocyte mobilization on the penumbral endothelium in CD1 mice subjected to controlled cortical impact using intravital microscopy (Lopez et al. 2022b). The mice received intraperitoneal injections of various dosages of propranolol ranging from 1 mg/kg to 4 mg/kg. The high-dose treatment (4 mg/kg) demonstrated a significant decrease in the number of rolling leukocytes at 48 hours post-injury compared to the saline group and low-dose treatment (1 mg/kg). To examine propranolol's effect over a longer timeframe, the same researchers conducted a separate study to measure leukocyte mobilization on the pial microvasculature 14 days after injury (Lopez et al. 2022a). Only the 4 mg/kg propranolol treatment group showed a reduced number of leukocytes rolling on the pial microvasculature. Thus, a high dose may be required to sustain propranolol's effect on leukocyte mobilization, which subsequently reduces leukocyte responses that can cause capillary injury and neuroinflammation. In fact, the reduction of cerebral proinflammatory cytokines including IL-1α, IL-1ß, IL-4, IL-17, and TNF- α associated with high-dose (4 mg/kg) propranolol treatment has been demonstrated previously in C57/Bl6 mice 24 hours

Table 2 SYRCLE's risk of bias assessment of included studies for systematic review

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Armstead and Vavilala 2019	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Genét et al. 2018	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Kota et al. 2016	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Larson et al. 2012	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Ley et al. 2012	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes
Ley et al. 2010	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
Ley et al. 2009	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Lopez et al. 2022a	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Lopez et al. 2022b	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Singer et al. 2023	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Wallen et al. 2022	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Yang et al. 2019	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Zeeshan et al. 2019	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Zlotnik et al. 2012	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes

* *D1* Sequence generation, *D2* Baseline characteristics, *D3* Allocation concealment, *D4* Random housing, *D5* Blinding (performance bias), *D6* Random outcome assessment, *D7* Blinding (Detection bias), *D8* Incomplete outcome data, *D9* Selective outcome reporting, *D10* Other sources of bias

after weight-drop induced TBI compounded with hemorrhagic shock (Wallen et al. 2022). However, targeting leukocyte responses represents only one potential mechanism of the neuroprotective effects of propranolol.

Accumulation of p-tau, through the generation of neurofibrillary tangles, has been linked to the development of chronic traumatic encephalopathy, Alzheimer's, and Parkinson's disease following TBI (Katsumoto et al. 2019; Padmakumar et al. 2022) A significant increase in p-tau accumulation in the hippocampus of C57/Bl6 mice subjected to weight-drop injury was observed using immunofluorescence (IF) and immunohistochemistry (IHC) (Singer et al. 2023). The accumulation was further enhanced by hemorrhagic shock following TBI compared to TBI only. Propranolol treatment significantly blunted p-tau accumulation 30 days after injury in both mice with TBI and TBI complexed with hemorrhagic shock. Not surprisingly, all the propranolol-treated groups from this study showed an improvement in the hippocampal-dependent Morrison Water Maze test 30 days after injury characterized by a reduction in time to raft after training (Singer et al. 2023). Furthermore, propranolol treatment was associated with higher novel object recognition scores by day 2 and the mice with TBI spent less time completing the maze at day 4 compared to the placebo group (Zeeshan et al. 2019). In addition, propranolol-treated (2, 4 mg/kg) mice demonstrated neurological improvements as early as 24 hours after injury, whereas low dose treatment (1 mg/kg) saw delayed improvements (36 hours after injury) in neurological functions (Lopez et al. 2022b). These results suggest that propranolol may improve memory, learning, and cognitive functions post-TBI in animal models through a number of possible mechanisms including preventing neuronal injury and cell death, leukocyte mobilization, and p-tau accumulation.

Neurological Functions Independent of Brain Barrier Permeability and Blood Glutamate Levels

A study investigated the therapeutic benefits of combining propranolol with an infusion of human mesenchymal stem cells in rats subjected to controlled cortical impact injury (Kota et al. 2016). Propranolol was associated with a decrease in the number of fully activated microglia in the injured brain, which would otherwise lead to further central inflammatory responses and neuronal cell death (Loane and Faden 2010). However, propranolol alone did not reduce blood brain barrier permeability. Another study investigated the effect of propranolol on edema in rats subjected to lateral fluid percussion injury, where edema was measured by brain water content and blood brain barrier permeability 24 hours after injury (Genét et al. 2018). Propranolol treatment had no effect on brain water content or blood brain barrier permeability. Conversely, an improvement in blood brain barrier integrity in propranolol-treated mice measured by reduced albumin leakage 24 hours after injury was observed (Lopez et al. 2022b). This correlated with a reduction in edema in the hemisphere ipsilateral to the injury. However, when measured 14 days after injury, the permeability of the pial microvasculature did not change in propranolol treated mice, regardless of the dose (1, 2, 4 mg/kg) (Lopez et al. 2022a). Therefore, propranolol's effect on blood brain barrier permeability appears to diminish over the course of treatment.

The influx of glutamate within the brain following TBI has previously been linked to neurotoxic effects (Baker et al. 1993; Zauner et al. 1996; Koura et al. 1998). When investigating the effects of propranolol on blood glutamate levels and the neurological outcomes of rats subjected to

closed head injury, decreasing blood glutamate levels were correlated with neurological improvement in motor functions and behaviour (Zlotnik et al. 2012). However, propranolol treatment prevented the blood glutamate levels from decreasing 60 minutes after injury compared to the saline-treated group. Both propranolol and saline treatments showed neurological improvements 60 minutes after injury.

Other Outcomes

Severe TBI has been linked to immunodeficiency characterized by decreased T lymphocyte counts (Mazzeo et al. 2006). The effects of propranolol on the peripheral immune system using Sprague-Dawley rats subjected to controlled cortical injury was examined (Yang et al. 2019). Specifically, the study investigated the expression of programmed cell death-1 (PD-1) and production of IFNg and TNFa by T cells. Twenty-four hours after injury, propranolol treatment reversed the elevation of PD-1-positive CD4+ and CD8+ T cells, which impaired T cell function and contributed to the dysfunction of B cells. Further, propranolol also increased the production of IFNg by CD4+ cells and TNFa by CD8+ cells, suggesting that propranolol may be able to attenuate the TBI-induced immunodeficiency.

Additionally, a study investigated the potential mechanism of propranolol's cardioprotective effects following TBI in rats subjected to controlled fluid percussion injury (Larson et al. 2012). Propranolol treatment decreased the level of reactive oxygen species in the left atrium and therefore may potentially mitigate damage to the myocardium caused by oxidative stress.

Discussion

In our systematic review, we observed that propranolol may be a potential treatment intervention in TBI. The effect of propranolol was evaluated for several reasons. First, it has been the most frequently studied beta-blocker in TBI patients. Many studies have demonstrated that propranolol may be superior to other beta-blockers in mitigating secondary injuries following TBI (Ley et al. 2018; Schroeppel et al. 2014) Propranolol has advantages given its lipophilicity and central nervous system penetration (Schroeppel et al. 2014). Our review demonstrates that the benefits of propranolol are not limited to counteracting the catecholamine surge following TBI. In the brain, propranolol may reduce secondary injury and improve cognitive function by increasing cerebral perfusion and preventing neuronal cell death, leukocyte mobilization and p-tau accumulation. Peripherally, propranolol may be able to attenuate the TBI-induced immunodeficiency by recovering T cell function, and mediate cardioprotective effects by reducing oxidative stress in the heart.

Limitations

Overall, the heterogeneity of TBI including differences in location and severity of injury as well as the species of the animal models hindered the reproducibility of the findings across studies. The animals differ biologically from humans which prevents a perfect model of the secondary injury development that occurs in human patients with TBI (Xiong et al. 2013). Both the mouse and rat models exhibit different physiological and behavioural responses to TBI (Fox et al. 1999; Reid et al. 2010). In addition, most TBI studies omit measurements of pCO2, pO2, blood pH or pressure, and body temperature, which can affect animal response to TBI and treatment. Furthermore, sex differences exist in animals used to study TBI. Specifically, estrogen has been shown to have a neuroprotective effect and is associated with less sequalae after TBI (Roof and Hall 2000). As a result, studies tend to choose biological males as the model system for TBI, thus leading to biases in sex (Lopez et al. 2022a, b; Wallen et al. 2022). For example, the changes that were observed in male mice in response to propranolol treatment were not observed in female mice (Singer et al. 2023). Therefore, findings from this review may lack generalizability of findings from animal studies to humans. In addition, there are differences in propranolol doses and routes of administration across studies. This can be problematic because propranolol's effects on cerebral autoregulation, neuronal cell death, and immunomodulation in human patients may vary widely depending on its dose. Therefore, human studies using standardized doses of propranolol are needed.

Implications for Future Research

TBI has been associated with cardiac dysfunction. Catecholamine surges have been associated with increased reactive oxygen species (ROS) (Singal et al. 1983), which in turn can cause necrosis of cardiomyocytes (Cruickshank et al. 1987; Neil-Dwyer et al. 1978). This is thought to contribute to development of new onset cardiomyopathy following TBI. Current standard of care for cardiovascular compromise following TBI is largely the same as other etiologies of heart failure – this involves hemodynamic support in the case of cardiogenic shock, provision of cardioprotective medications like angiotensin-receptor blockers and beta blockers. Therefore, propranolol may be an ideal agent for treating cardiac dysfunction associated with TBI by decreasing myocardial ROS levels (Larson et al. 2012).

Moreover, TBI has also been associated with relative immunodeficiency as evidenced by increased incidence of infections in TBI populations. The nature of this immunodeficiency is not yet well understood, although some studies suggest that T cell function may be compromised. There is no established treatment to address this immunodeficiency. Animal studies

suggest that TBI-induced immunodeficiency may be reversed by recovery of T cell function by administering propranolol. Further studies of propranolol in human T-cells are needed in order to confirm whether this phenomenon is also seen in humans. One way to reduce morbidity and mortality in TBI would be by reducing infectious complications, which may be achieved by propranolol's restoration of immune function.

Conclusion

In our systematic review of preclinical studies of TBI models, it was observed that propranolol may be a potential therapeutic intervention to consider in TBI. Propranolol potentially mediates its therapeutic effects in the brain by increasing cerebral perfusion and decreasing neuronal cell death, leukocyte mobilization, and p-tau accumulation; and peripherally by regulating T lymphocyte response and levels of reactive oxygen species. However, this review may be limited by the lack of generalizability of findings from animal studies to humans and the heterogeneity of TBI. Before propranolol can be considered in clinical practice, well-designed trials in TBI patients should be performed to evaluate the effect of propranolol.

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Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

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Conflicts of Interest/Competing Interests The authors declare no competing interests.

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