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Drug-induced-acute liver failure: A critical appraisal of the thioacetamide model for the study of hepatic encephalopathy

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ABSTRACT

Hepatic encephalopathy (HE) following acute and chronic liver failure is defined as a complex of neuropsychiatric abnormalities, such as discrete personal changes, sleep disorder, forgetfulness, confusion, and decreasing the level of consciousness to coma. The use and design of suitable animal models that represent clinical features and pathological changes of HE are valuable to map the molecular mechanisms that result in HE. Among different types of animal models, thioacetamide (TAA) has been used extensively for the induction of acute liver injury and HE. This agent is not directly hepatotoxic but its metabolites induce liver injury through the induction of oxidative stress and produce systemic inflammation similar to that seen in acute HE patients. In this short review article, we shortly review the most important pathological findings in animal models of acute HE following the administration of TAA.

1. Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that is a consequence of acute and chronic liver failure (ACLF) or cirrhosis. Symptoms of HE become apparent depending on the primary cause of the existing liver injury and may include: anxiety, shortened attention span, sleep problems, lethargy, personality change, confusion, forgetfulness, and other serious complications until coma [1]. Patients with ALF have type A HE that can progress to a severe form that is life-threatening due to cerebral edema and intracranial hypertension [2]. As the pathogenesis of HE and cerebral edema is not fully understood an experimental model would be highly valuable to explore the pathological changes at a molecular level. The optimal animal model of HE should include (i) reversibility by appropriate treatment, (ii) reproducibility for induction of coma and for increasing the brain water content/ intracranial pressure, (iii) degree of liver failure, (iv) provide a therapeutic window [3] (Table 1).

Several chemical agents have been utilized for the induction of HE following ALF (Table 1). Acetaminophen, galactosamine, and lipopolysaccharide are pharmacological agents that are used for the induction of

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AQP4, aquaporin 4 water channel; BBB, blood-brain barrier; B7, B7 molecules (CD80+CD86); CBF, cerebral blood flow; CCL2, chemokine ligand 2; CNS, central nervous system; CTLA4, Cytotoxic T-lymphocyte-associated Protein 4; CYP2E1, Cytochrome P450 family 2 subfamily E member 1; GFAP, glial fibrillary acidic protein; HE, hepatic encephalopathy; Iba1, ionized calcium-binding adaptor molecule 1; IL-β, interleukin 1 β; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; OA, L-ornithine-L-aspartate; NAC, N-acetylcysteine; NF-κB, nuclear factor κB; TAA, thioacetamide; ROS, reactive oxygen species; TASO, thioacetamide sulfoxide; $TASO_2$, thioacetamide sulfdioxide; TLR-2, toll-like receptor 2; TLR-4, toll-like receptor 4; TNFα, tumor necrosis factor α.

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HE but they are not reproducible because the pathological features of these components have not resembled those seen in HE patients and neuropathological changes are also very variable in different species [4]. For example, some neurological deficits in a low dose of acetaminophen have been reported [5]. Furthermore, there is a diversity in the induction of ALF between male and female mice after injection of acetaminophen. Female mice usually are more resistant to liver injury compared to male mice following the injection of acetaminophen [6]. Acetaminophen causes severe injury in liver sinusoidal endothelial cells and hypovolemic shock that these changes are different from ALF patients [7]. On the other hand, galactosamine and lipopolysaccharide have a short therapeutic window, and their pathological consequences, such as severe permeabilization of the blood-brain barrier (BBB) and cerebral tissue necrosis have not been seen in patients with ALF [4,8]. Galactosamine causes a variety of involvement of multiple organ diseases, such as renal failure and lung injury, and doesn't have specific ALF pathological features [9,10]. Also, azoxymethane and lipopolysaccharide are rarely used for animals larger than mice, due to their high cost and hazards [11,12]. Thioacetamide (TAA) has been widely used in the HE animal model because it is a reproducible model in many animal species, such as mice, rats, and guinea pigs that can induce liver injury that mimics ALF and HE as seen in patients. Furthermore, TAA provides a time window as in human ALF that makes it optimal to do experimental studies of HE.

TAA with molecular formula C_2H_5NS is an organosulfur compound that was recognized first as a hepatotoxic agent in rats by Fitzhugh and Nelson in 1948 [13]. To induce ALF and acute HE, high doses of TAA should be administrated in a short time according to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism guidelines [4], while chronic low dose administration of TAA for 3–4 months may be valuable to induced cirrhosis and development of liver tumors [14–17]. In this study, we review in more detail the pathological changes found after high doses of TAA administration in mice and rats.

The dose must have been delivered in a short time

2. Pathological consequences of TAA administration

2.1. Peripheral effects

2.1.1. Liver injury

TAA metabolites produce oxidative stress and cause liver injury [39,40] (Box 1). Injection of TAA intraperitoneally in mice causes a significant increase in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin [26,41–44] indicates the destruction of the hepatocyte cell membrane [45]. Moreover, TAA may also induce histopathological changes, such as cell apoptosis, pre-portal inflammation, and periacinar hemorrhage [26,41,43,46]. Liver injuries induced by TAA are very predominant in rats and histological damages, such as infiltration of neutrophils and lymphocytes, sinusoidal congestion, sinusoidal hemorrhage, centrilobular necrosis, pigmentation, and hepatocyte vacuolation are observed followed by TAA injection in rats [36,47–53] (Box 2).

2.1.2. Hyperammonemia

Ammonia with the molecular formula NH_3 is a nitrogenous compound that is produced by gut bacteria, enterocytes, and renal tubules via glutaminase enzyme. Under liver failure induced by TAA, ammonia cannot be converted into urea and is released from the hepatic veins into the systemic circulation causing hyperammonemia (Fig. 1). The exact mechanism underlying the neurotoxicity of HE remains unclear. Ammonia is a well-known neurotoxin and is a key molecule that is involved in the pathogenesis of HE [54–57]. The persistence of hyperammonemia aggravates the degree of HE as results in the brain in human ALF while a reduction of the blood levels of NH3 alleviates HE [58]. Among the several toxins suggested, the case for ammonia is most convincing [57]. Events that lead to increased levels of blood or brain ammonia have been revealed to worsen HE, whereas reducing blood ammonia levels improves HE [59–61]. One of the great advantages of TAA is the increasing levels of ammonia in the systemic circulation [26,62,63], liver [50], and cerebral tissue [26,50,64] what has been seen in ALF patients [26]. Clinical, pathological, and biochemical alterations observed in HE can be mimicked by increasing blood or brain ammonia levels in experimental TAA models. The level of ammonia has been increased more than two-fold in animals treated with TAA [26]. Moreover, the severity of encephalopathy was also shown to correlate well with blood and brain ammonia levels in animal models of TAA [26,65,66]. This grading of severity is similar to that seen in HE patients [26,59].

2.1.3. Systemic inflammation

The issue of peripheral inflammation as an important contributor to HE has received considerable critical attention. A growing body of evidence now indicates that ammonia and inflammation synergistically regulate the onset and severity of HE [67,68]. Following hepatocyte injury by TAA, the production of reactive oxygen species (ROS) activates downstream signals, such as c-Jun N-terminal kinase (JNK) and caspase 3. These signaling pathways lead to mitochondrial dysfunctions and the induction of apoptosis in hepatocytes [69]. Injured hepatocytes release damage-associated molecular patterns (DAMPs), S100 proteins, and highmobility group box proteins (HMGBs) with a toll-like receptor 2 (TLR-2) and toll-like receptor 4 (TLR-4) dependent mechanism manner that activates hepatic macrophages called Kupffer cells [70,71] (Fig. 1). Activated Kupffer cells release pro-inflammatory cytokines and increase further liver injury [72]. Besides hyperammonemia, these pro-inflammatory cytokines are released into the blood circulation and activate the circulatory neutrophils. DAMPs are generated from the injured liver that activates the circulatory monocytes [73]. Circulatory activated monocytes and neutrophils also stimulate the expression of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [74]. The severe cytokine storm in the TAA model was comprehensively investigated by Li-Qing Wang and colleagues. They showed that the expressions of IL-1β, IL-6, and TNF-α in plasma and brain significantly increased in TAA rats [75]. In addition to IL-6, TAA injection increases the concentration of serum cytokines, such as IL-1β and chemokine ligand 2 (CCL2) in mice [26,76] (Fig. 1). Likewise, TAA activates the nuclear factor κB (NF-κB) in the mice liver [77].

Table 1
Comparison of some chemical agents for inducing animal models of ALF according to Terblanche and Hickman criteria.

Agents	Species	Reversibility	Reproducibility	Death from liver failure	Therapeutic window	Animal size	No hazard	References
Acetaminophen	Pig, dog, rabbit, rat, mouse	✓	×	✓×	✓×	✓✓	✓✓	[18,19,20,21,22,23]
Azoxymethane	Mouse	✓	✓✓	✓	✓	×	×	[24,25,26,27]
Galactosamine	Pig, dog, rabbit, rat, mouse	✓	×	✓✓	×	✓✓	×	[23,28,29]
Lipopolysaccharide	Rat, mouse	✓	×	✓	×	×	×	[30,31,32]
Thioacetamide	Guinea pig, rat, mouse	✓	✓	✓✓	✓✓	✓	×	[26,33,34,35,36,37,38]

Box 1
Cytochrome P450 family 2 subfamily E member 1 mediates hepatotoxic effects of TAA

Cytochrome P450 family 2 subfamily E member 1 (CYP2E1) is a member of the cytochrome P450 superfamily that plays an important role in the breakdown of many toxins that have entered the body. This protein is responsible for the oxidation of TAA to its metabolites in the liver. In the first step, CYP2E1 metabolizes TAA to thioacetamide sulfoxide (TASO) and then to its hepatotoxic and highly reactive metabolite thioacetamide sulfoxide ($TASO_2$) [39]. Liver injury is induced by this reactive metabolite as a free radical when it covalently binds to the liver lipids and proteins [39,83].

$$CH_3CSNH_2(TAA) \xrightarrow{CYP2E1} CH_3CSONH_2(TASO)$$

$$CH_3CSONH_2 \xrightarrow{CYP2E1} CH3CSO_2NH_2(TASO_2)(\text{Hepatotoxic metabolite})$$

Box 2
Strategies for successfully establishing acute hepatic encephalopathy by TAA

Thioacetamide usually is packaged in bottles as a white or yellowish powder. This agent dissolves easily in water and/ or 0.9 % sodium chloride. To achieve the best results of the HE model using TAA, the concentration of TAA, the number of injections, and animal body weight should be mentioned. For instance, two and three consecutive injections of TAA at doses of 100, 300, and 350 mg/kg, could induce liver injury, hyperammonemia, systemic inflammation, BBB disruption, and CNS damage [26,75,116,142]. Also, a single injection with doses of 300, 600, or 1200 mg/kg are another widely used method for inducing HE [43,50]. Daily assessment of neurological scores and grades of encephalopathy can help to monitor the progression of the disease. To decrease the manifestations of hypoglycemia, hypovolemia, and dehydration, easy access to food on the cage floor, and injections of 5% dextrose and 0.45 % NaCl subcutaneously and daily control of body temperature are essential in animals [115,132].

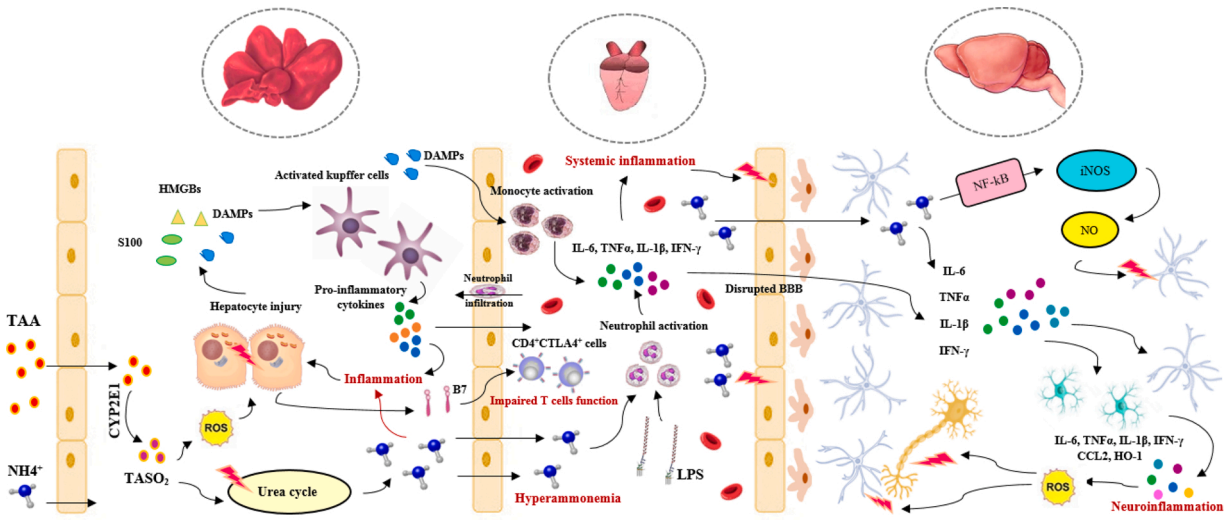

Fig. 1. Schematic representation of cascades that may involve the induction of hepatic encephalopathy by thioacetamide. Acute injection of thioacetamide intraperitoneally leads to liver injury through an increase in the production of oxidative stress and inflammation. The dysfunctional liver cannot eliminate blood-borne toxins such as ammonia and lipopolysaccharides from circulation. These agents produce systemic inflammation through the activation of the circulatory monocytes and neutrophils. Ammonia and other toxic agents then reach the brain and cause pathological changes such as neuroinflammation, gliopathy, neuropathy, cerebral edema, intracranial hypertension, and brain herniation. Abbreviations: BBB: blood-brain barrier; B7: B7 molecules (CD80 + CD86); CCL2: C—C Motif Chemokine Ligand 2; CTLA4: Cytotoxic T-lymphocyte-associated Protein 4; CYP2E1: cytochrome P450 family 2 subfamily E member 1; DAMPs: damage-associated molecular patterns; HMGBs: high-mobility group box proteins; HO-1: heme oxygenase 1; IFN-γ: interferon γ; IL-1β: interleukin 1β; IL-6: interleukin 6; iNOS: inducible nitric oxide synthetase; LPS: lipopolysaccharide; $NH4^+$: ammonia; NF-kB: nuclear factor-kB; NO: nitric oxide; ROS: reactive oxygen species; S100: S100 proteins; TAA: thioacetamide; $TASO_2$: thioacetamide sulfoxide; TNFα: tumor necrosis factor α.

Similarly, TAA can increase the expression of pro-inflammatory cytokines in blood circulation and increase the level of NF-κB, heme oxygenase-1, TNF-α, and IL-6 in the rat liver [78–80]. Furthermore, it has been reported that the levels of soluble B7 molecules significantly increased in primary hepatocyte culture supernatants and serum of patients with ALF [81]. These molecules through interaction with cytotoxic T lymphocyte-associated protein 4 (CTLA4) modulate T cell activation [82]. In patients with ALF, B7 molecules are secreted from the failing liver that leads to the expression of CTLA4 on circulatory $CD4^+$ cells and causes impairment of T cell function [81]. Overall, the most obvious findings to emerge from these studies are that TAA can induce ALF and causes systemic inflammation which is similar to that seen in HE patients.

2.2. Cerebral effects

2.2.1. Blood-brain barrier

The BBB is a selective structure that is indispensable for preventing the entry of neurotoxic substances into the central nervous system (CNS). BBB includes the basement membrane, endothelial monolayer, pericytes, and astrocyte end-feet. Any pathological alternation in each of these components can disrupt the integrity of BBB [84]. Kato and colleagues with an ultrastructural analysis of the cerebral cortex in nine ALF patients confirmed swelling of astrocytes end-feet and increasing of the number of vacuoles and vesicles in endothelial cells and pericytes. They also reported that the basement membrane was vacuolized while thigh junctions between endothelial cells were intact [85]. These findings indicate the disruption of BBB in ALF is physiochemical in nature compared to structural changes.

Another way of BBB permeabilization by TAA is the peripheral changes, such as the increased plasma level of ammonia, lipopolysaccharides, and pro-inflammatory cytokines that reach the BBB and cause the breakdown of this protective barrier against circulating toxins [26,86,87]. Experiential studies indicate that TAA exacerbates the permeability coefficient of an in vitro BBB model [26] and increases the level of Evans blue dye in the brain tissue of mice indicating BBB disruption [26,88]. However, other studies in rats with ALF induced by TAA have reported no significant changes in the level of Evans blue dye in the brain tissue [89]. Furthermore, the protein expression of claudin-5 and occludin, as two main proteins in the structure of BBB, were not significant between control and TAA rats [90].

2.2.2. Cerebral blood flow

Cerebral autoregulation is a homeostatic process that adjusts and keeps cerebral blood flow (CBF) constant during variations in arterial blood pressure [91]. Disrupted autoregulation causes metabolic impairment of the neural cells and induces cerebral ischemia [91,92]. Many studies have been shown that autoregulation of CBF is decreased or even lost under liver failure conditions and HE patients [93–99]. Importantly, neuropsychiatric symptoms that appear in HE are correlated with impairment of CBF [100,101]. Interestingly, these cerebral changes have been seen in TAA-induced HE rats. For instance, Larsen et al. reported that autoregulation of CBF in the TAA model disappears when the arterial blood pressure is manipulated as the results of injection of norepinephrine and venesection similar to that seen in HE patients [102]. Furthermore, a significant reduction in CBF and cerebral oxygen consumption was observed in TAA-induced HE rats [103].

2.2.3. Neuroinflammation

Ammonia can cross the BBB through ion transporters (in the form of NH_4^+) and by passive diffusion (in the form of NH_3) [104]. Ammonia in the brain parenchyma triggers the activation of microglia in the CNS. Activated microglia releases IL-6 and TNFα which can result in gliopathy and neurodegeneration (Fig. 1). Furthermore, ammonia with activation of toll-like receptor 4 on endothelial cell membrane triggers the production of cytokines [105]. The use of TAA as a hyperammonemia model transforms the resting phenotype of cortical microglia to an activated phenotype with round cell bodies and long processes [26,76]. Furthermore, TAA significantly increases the concentration of CCL2 in the cerebral cortex [26]. Similarly, TAA enhances the concentration of pro-inflammatory cytokines, such as IL-6, IL-1β, TNFα, CCL2, and NF-κB in the brain of rats [65,75,106]. In addition, the expressions of cerebral proinflammatory cytokines were positively correlated with brain water content but negatively correlated with motor activity counts [75]. Also, the expression of ionized calcium-binding adaptor molecule 1 (Iba1) as a marker for microglia increases after acute injection of TAA in the cerebral cortex of rats [106,107]. It has been shown that the number of glial fibrillary acidic protein (GFAP+) cells as an index of neuroinflammation has increased two-fold in the TAA group compared to the control group [42].

2.2.4. Gliopathy

Glial cells are non-neuronal cells of the CNS which provide protection for neural cells and maintain homeostasis of the nervous system. The main glia in the CNS including microglia, astrocyte, and oligodendrocyte. Microglia with the production of inflammation and the ability for phagocytosis plays an important role in tissue repairing following brain injuries. Astrocytes are the supporting cells of CNS that prepare nutrients for neurons and preserve them from ammonia toxicity (the only cell type in CNS that contains glutamine synthetase) and other neurotoxic agents [108]. Evidence shows that TAA affects the function of glial cells in the CNS [42,109,110]. Injection of TAA increases the expression of the GFAP as a marker for astrogliosis in the hippocampus and cerebellum in mice [42,111]. Furthermore, the expression of Iba1 as a marker for microglia significantly increased in the cerebral cortex of rats when treated with TAA [26,106]. Likewise, TAA induces astrocyte swelling in the frontal cortex, cerebellum, hippocampus, and pons in rats [76,112,113] [107]. However, the effect of TAA on glial cell behavior is not fully understood; further studies on this topic are warranted.

2.2.5. Brain edema

One of the life-threatening complications of ALF is cerebral edema. This complication can lead to brain herniation followed by intracranial hypertension. Hyperammonemic conditions and neuroinflammation disturb the glia functions and cause neuronal injuries [114]. Mechanisms of brain edema in ALF remain fully understood. One widely used technique for the assessment of brain edema in animal models is the measurement of brain water content. In this protocol, some pieces of the brain cortex are weighed and dried in an oven overnight and then weighed again. The percentage of brain water content calculates the following formula: [(wet weight - dry weight)/ wet weight]×100 [115]. Acute injection of TAA increases the brain water content and induces brain edema in mice [26]. Furthermore, TAA enhances the brain water content in a neuroinflammation and ammonia-dependent manner in rats [36,75,116]. Aquaporin 4 water channel (AQP4) is the main water channel responsible for water efflux in CNS [117,118]. The expression of this channel in animal models of HE is controversial. For example, it has been reported that TAA-induced acute HE increased the expression of AQP4 and brain edema in the cerebral cortex [116], while in another study, even though the brain water content had been increased but the expression of AQP4 had not changed [119]. This discrepancy may be related to the stages of cerebral edema. In cytotoxic edema, cell swelling is mainly present in astrocytes and the BBB remains intact while in vasogenic edema, the permeability of BBB increases, and net flux of water and blood constituents occur into the extracellular space [120].

2.2.6. Neurological alternations

Patients with liver failure show degrees of motor changes, attention deficits, and cognitive impairment [121]. In mice with ALF following injection of TAA, locomotion score [36,111] and grip strength significantly decreased while ataxia coefficient [26] increased compared to the control group. Cognitive function was also impaired in these mice [111]. Furthermore, in the TAA group, the motor activity score [122], falling latency time in the rotarod test, and exploratory behavior in open field apparatus [65] decreased compared to the control group in rats. Also, all reflexes such as withdrawal, grasping, corneal, auditory startle, head shake, and righting reflex significantly decreased in these rats [107]. Surprisingly, TAA causes several key pathophysiological changes that are seen in HE patients (Table 2).

3. TAA-induced HE model and pharmacological studies

Pharmacological interventions are developing to relieve the main outcomes in HE patients. To figure out the underlying mechanisms in drug development, an appropriate animal model should be considered. To this point, the review of the most effective drugs used in clinical grades on TAA models can provide us a valuable platform for testing

Table 2
Symptoms of HE patients in comparison with TAA-induced HE.

Symptoms of HE patients	TAA-induced HE model	References
Hypovolemia	✓	[111,123,124]
Hypokalemia	✓	[111,123]
Hypoglycemia	✓	[111,119,123,125]
Hypoxia	✓	[126,127]
Lack of awareness	×	–
Euphoria	×	–
Lethargy or Apathy	✓	[75,125,128,129,130,131,132]
Dyspraxia	×	–
Asterixis	×	–
Reduced alertness	✓	[128,129,131]
Irritability	×	–
Cognitive impairment	✓	[111,133,134,135,136]
Forgetfulness and memory problems	✓	[133,137]
Motor function impairment	✓	[26,62,75,125,136]
Slurred speech	×	–
Anxiety	✓	[132,138]
Balance problems	✓	[26,75,123,125,128,129]
Personality changes	×	–
Shortened attention span	×	–
Myoclonus (muscle twitches)	×	–
Altered sleep rhythm and EEG abnormality	✓	[139,140,141]
Coma	✓	[26,75,119,128]

potential therapeutic strategies for HE. In this outline, we reviewed and summarized the results of some effective drugs that have been investigated on TAA models and applied in clinical grades.

L-ornithine-L-aspartate (OA) composes of ornithine and aspartic as natural amino acids. Data from experimental and clinical studies have shown that OA relieves some symptoms of HE by decreasing hyperammonemia [58,143,144]. Since TAA can cause alterations in cell permeability in liver cells [145], direct action of OA on liver cell leakage was investigated in the TAA model [146]. TAA-induced pathogenic changes in the levels of biochemical parameters (i.e., AST, ALT, and alkaline phosphatase levels) were notably improved by the OA treatment [146]. Furthermore, OA improved motor activity, grip strength, and severity of disease in TAA-induced HE in mice [147].

Lactulose and rifaximin are widely used for the treatment of HE patients [148]. Lactulose, a non-absorbable disaccharide, decreases the breakdown of nitrogenous compounds to ammonia with acidification of the intestinal tract [149]. It has been shown that TAA-induced pathogenic changes in the levels of blood AST, ALT, and ammonia were significantly improved by lactulose treatment [150,151]. Moreover, a significant improvement in survival rate, sensory behavior, and motor activity was observed by lactulose treatment in TAA-induced HE rats [150]. Furthermore, lactulose significantly reduced the level of total bilirubin and increased the concentration of albumin in TAA-induced HE [152]. Rifaximin, a broad-spectrum antibiotic, decreases the production and absorption of intestinal ammonia by affecting the population of gut flora; therefore, this intervention leads to a significant increase in the level of portal ammonia in HE [153]. Likewise, the administration of rifaximin significantly decreased the concentrations of AST and ALT as well as the level of serum ammonia in TAA-induced acute HE rats [154].

Indomethacin and N-acetylcysteine represent acceptable results in ALF patients [155,156]. Indomethacin is a nonsteroidal anti-inflammatory drug that has beneficial effects in uncontrolled intracranial pressure following acute liver failure [157,158]. N-acetylcysteine (NAC) is a first-line treatment for acetaminophen hepatotoxicity [159,160]. However, it is also suggested for non-acetaminophen-induced ALF patients [161]. Administration of NAC prevents the outcome of HE from worsening and decreases the duration of hospitalization in ALF patients [162–164]. The precise mechanisms of NAC in ALF patients remain unclear. However, antioxidant and anti-inflammatory properties have been previously reported [165,166]. NAC improves liver function tests, serum pro-inflammatory cytokines, and oxidative stress in TAA-induced ALF and HE [151,167,168]. Taken together, TAA imitates some critical aspects of HE pathogenesis; therefore, it is a reasonable model for drug development in the context of HE.

4. Conclusion

Administration of high doses of TAA intraperitoneally is an efficient model for studying HE pathogenesis. This agent acutely increases the level of liver, plasma, and brain ammonia that can induce systemic inflammation and neuroinflammation. Therefore, this model can be introduced as a valid model for studying the mechanisms of neuroinflammation and microglia activation under hyperammonemia conditions. Furthermore, the pathological processes that are involved in astrocyte swelling and brain edema can be investigated by the acute injection of TAA in mice and rats. However, the BBB seems less affected by TAA as seen in human ALF [85]. All of the pathophysiological alterations in the liver, circulation, and within the brain after TAA intoxication grossly mimic changes seen in human ALF. These make this model attractive for future studies of the devastating effects of severe HE.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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