from mild, to moderate, to severe, and may be focal or diffuse. Focal injuries occur in a specific location whereas diffuse injuries are associated with potentially widespread axonal dysfunction and vascular damage.

[0006] Damage to the brain from TBI occurs in two phases. The initial primary phase is the head trauma event itself, which is irreversible and amenable only to preventative measures to minimize the extent of damage, followed by an ongoing secondary phase, which begins at the time of injury and continues in the ensuing days to weeks to years. This secondary phase leads to a variety of physiological, cellular, and molecular responses aimed at restoring the homeostasis of the damaged tissue, which may lead to secondary brain injury.

[0007] There exists a need in the art for pharmaceutical agents to treat diseases responsive to the modulation of pro-inflammatory mediator expression.

BRIEF SUMMARY OF THE INVENTION

[0008] Applicant has unexpectedly found that acetyl-L-leucine modulates the expression of pro-inflammatory mediators in a control cortical impact induced (CCI) traumatic brain injury model in mice. Thus, in one aspect, the present disclosure refers to the use of a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating the expression of one or more pro-inflammatory mediators in a subject with a traumatic brain injury. In one example, there are disclosed methods of treating a disease, disorder, condition, or syndrome wherein the modulation of one or more pro-inflammatory mediators provides a benefit. Foremost among these diseases, disorders, conditions, or syndromes are neuroinflammatory, neurological, autoimmune, neurodegenerative proteinopathic, psychiatric, and mitochondrial diseases, disorders, conditions, or syndromes.

[0009] Without wishing to be bound by any particular theory, it is believed that leucine, acetyl-DL-leucine, acetyl-D-leucine, and acetyl-L-leucine modulate neuroinflammation which is a pathway to combat the molecular cascades contributing to neuroinflammatory and other diseases, disorders, conditions, or syndromes. For example, secondary brain injury in TBI patients may be characterized by a hyper-reactive response, where an excess of pro-inflammatory cytokines may play a role in maintenance of brain function as well as repair after TBI. Head-trauma induced brain injury may trigger excessive and/or uncontrolled release of these cytokines, particularly interleukin (IL)-1β, IL-6, and tumour necrosis factor (TNF)-α, which may result in significant brain damage. Pro-inflammatory cytokines are

reported to play a role in the pathophysiology of neurodegenerative diseases such as AD, MS, PD, and ALS (Wei-Wei et al., *Mol. Med. Rep.* 2016; 13(4):3391-3396), and have been identified to be a hallmark of genetic-neurodegenerative disorders such as GM1 and GM2 gangliodises (Jeyakumar et al., *Brain* 2003; 126(Pt 4):974-87). In addition, disruption of normal lysosomal function in the lysosomal storage diseases (LSDs) has been associated with abnormalities in inflammation, such as abnormally elevated pro-inflammatory cytokines. (Simonaro, *Journal of Inborn Errors of Metabolism & Screening*, Vol. 4: 1-8 (2016)).

[0010] Also, without wishing to be bound by any particular theory, it is also believed according to the present disclosure that DL-leucine, L-leucine, D-leucine, L-leucine ethyl ester, acetyl-DL-leucine, acetyl-D-leucine, and acetyl-L-leucine modulates microtubule-associated protein Tau (which is an autophagy substrate) and/or the microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate (LC3-II), which may be markers of TBI. LC3-II is a marker of autophagosome formation, and increased levels of LC3-II can reflect impaired clearance of autophagic vacuoles. Autophagosomes are formed, but are not cleared. Autophagy is impaired in AD, and AD brains exhibit increased levels of LC3-II.

[0011] In another aspect, the present disclosure refers to the use of a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a traumatic brain injury in a subject in need thereof, or treating a symptom of a traumatic brain injury in a subject in need thereof. In one example, there are disclosed methods of treating a disease, disorder, condition, or syndrome in a subject in need thereof, or treating a symptom of a disease, disorder, condition, or syndrome in a subject in need thereof, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject, wherein the diseases, disorders, conditions, or syndromes are any one or more of the diseases listed in Tables 1-17, see below. A "Compound of the Disclosure" collectively refers to DL-leucine ("DLL"), L-leucine ("LL"), D-leucine ("DL"), L-leucine ethyl ester ("LLE" or "LEE"), acetyl-DL-leucine ("ADLL"), acetyl-D-leucine ("ADL"), or acetyl-L-leucine ("ALL," "NAL", or "NALL"), and the pharmaceutically acceptable salts thereof.

[0012] In one example, the present disclosure describes methods of treating TBI in a subject in need thereof, or treating a symptom of TBI in a subject in need thereof, the method comprising administering a therapeutically effective amount a Compound of the Disclosure to the subject.

[0013] In another example, the present disclosure describes a Compound of the Disclosure for use in treating a disease, disorder, condition, or syndrome in a subject in need thereof, or for use in treating a symptom of a disease, disorder, condition, or syndrome in a subject in need thereof, wherein the diseases, disorders, conditions, or syndromes are any one or more of the diseases listed in Tables 1-17, see below.

[0014] In another example, the present disclosure describes a Compound of the Disclosure for use in treating TBI in a subject in need thereof, or for use in treating a symptom of TBI in a subject in need thereof.

[0015] In another example, the present disclosure describes the use of a Compound of the Disclosure for the manufacture of a medicament for treating a disease, disorder, condition, or syndrome in a subject in need thereof, or for the manufacture of a medicament for treating a symptom of a disease, disorder, condition, or syndrome in a subject in need thereof, wherein the diseases, disorders, conditions, or syndromes are any one or more of the diseases listed in Tables 1-17, see below.

[0016] In another example, the present disclosure describes the use of a Compound of the Disclosure for the manufacture of a medicament for treating TBI in a subject in need thereof, or for the manufacture of a medicament for treating TBI in a subject in need thereof.

[0017] In another example, the present disclosure describes a pharmaceutical composition comprising a Compound of the Disclosure and a pharmaceutically acceptable carrier for use in treating a disease, disorder, condition, or syndrome in a subject in need thereof, or for use in treating a symptom of a disease, disorder, condition, or syndrome in a subject in need thereof, wherein the diseases, disorders, conditions, or syndromes are any one or more of the diseases listed in Tables 1-17, see below.

[0018] In another example, the present disclosure describes a method of modulating the expression of pro-inflammatory mediators, e.g., pro-inflammatory cytokines and pro-inflammatory chemokines in a subject in a subject in need thereof, the method comprising administering a therapeutically effective amount a Compound of the Disclosure to the subject. In another example, the pro-inflammatory mediators include, but are not limited to, NOS2, IL-18, IFNb, IL-1β, TNFα, NOX2, NLRP3, SOCS3, ARG1, IL-10, IL-4ra, and/or YM1.

[0019] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

WHAT IS CLAIMED IS:

1. Use of a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a traumatic brain injury in a subject in need thereof, or treating a symptom of a traumatic brain injury in a subject in need thereof.

2. The use of claim 1, wherein about 1 g to about 30 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

3. The use of claim 2, wherein about 2 g to about 15 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

4. The use of claim 3, wherein about 3 g to about 10 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

5. The use of claim, wherein about 4 g to about 8 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

6. The use of claim 5, wherein about 4 g to about 5 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

7. The use of claim 6, wherein about 5 g of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject per day.

8. The use of any one of claims 1-7, wherein a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject to treat the traumatic brain injury.

9. The use of any one of claims 1-7, wherein a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, is to be administered to the subject to treat the symptom of a traumatic brain injury.

10. Use of a therapeutically effective amount of acetyl-L-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating the expression of one or more pro-inflammatory mediators in a subject with a traumatic brain injury.

11. The use of claim 10, wherein the one or more pro-inflammatory mediators are NOS2, IL-18, IFNb, IL-1β, TNFα, NOX2, NLRP3, SOCS3, ARG1, IL-10, IL-4ra, or YM1.