Therapeutic Agents for Neurodegenerative Diseases

This application claims priority benefit to UK 1613829.9, filed August 11, 2016, UK 1702551.1, filed February 16, 2017, UK 1705766.2, filed April 10, 2017, and UK 1706867.7, filed April 28, 2017; all of which are incorporated herein by reference in their entirety.

Neurodegenerative diseases are those that affect neurons. The degenerative process can involve the progressive loss of neuronal structure, the progressive loss of neuronal function, or progressive neuron cell death. Such progressive neurodegeneration often results in physical disability and mental deterioration. Many neurodegenerative diseases are severely progressive and unremitting, and there are few, if any, curative treatments.

Although the process of neurodegeneration is not fully understood, therapeutic agents that are shown to be broadly neuroprotective are thought to be applicable to neurodegenerative diseases generally. In addition, many neurodegenerative diseases are associated with lysosomal dysfunction. This includes both neurodegenerative lysosomal storage disorders (LSDs) and many other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, where links to lysosomal defects have been suggested.

The present disclosure addresses a need to develop improved and widely applicable treatments for neurodegenerative diseases. In particular, the present disclosure describes acetyl-leucine for treating a neurodegenerative disease or one or more symptoms of a neurodegenerative disease in a subject. The neurodegenerative disease may, but need not, be associated with lysosomal dysfunction.

In one aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the neurodegenerative disease is chosen from Alzheimer's disease, ALS, MSA-P, MSA-C, frontotemporal dementia with parkinsonism, progessive supranuclear palsy, corticobasal degeneration, cerebellar downbeat nystagmus, Lewy Body dementia, and ataxia telangiectasia (Louis Barr disease), and wherein acetyl-leucine, or a pharmaceutically acceptable salt thereof

is to be administered at least two times a day to achieve a total daily dose of from about 0.5 g to about 15 g.

In one embodiment, there is disclosed acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the neurodegenerative disease is not cerebellar ataxia or Niemann-Pick type C disease.

Claims:

1. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the neurodegenerative disease is chosen from Alzheimer's disease, ALS, MSA-P, MSA-C, frontotemporal dementia with parkinsonism, progessive supranuclear palsy, corticobasal degeneration, cerebellar downbeat nystagmus, Lewy Body dementia, and ataxia telangiectasia (Louis Barr disease), and wherein acetyl-leucine, or a pharmaceutically acceptable salt thereof is to be administered at least two times a day to achieve a total daily dose of from about 0.5 g to about 15 g.

2. The use according to claim 1, wherein the subject is asymptomatic.

3. The use according to claim 2, wherein the subject has been found to have a genetic and/or biochemical marker of the neurodegenerative disease.

4. The use according to claim 1, for delaying the onset of a neurodegenerative disease or one or more symptoms of a neurodegenerative disease that would otherwise be expected to manifest according to typical disease progression.

5. The use according to claim 1, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

6. The use according to claim 1, for delaying the progression of a neurodegenerative disease or one or more symptoms associated with a neurodegenrative disease over time as compared to typical disease progression, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

7. The use according to claim 1, for reversing the progression of a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease over time, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the

subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

8. The use according to claim 1, for improving in a subject in need thereof a biochemical marker of a neurodegenerative disease over time, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

9. The use according to claim 8, wherein the biochemical marker is increased lysosomal volume.

10. The use according to any of claims 1-9, wherein a therapeutically effective amount of acetyl-leucine is to be administered to the subject in need thereof when the subject is asymptomatic.

11. The use according to claim 10, wherein the therapeutically effective amount of acetyl-leucine is to be administered after the subject has been found to have a genetic and/or biochemical marker of the neurodegenrative disease.

12. The use according to any of claims 1-4, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

13. The use according to any of claims 1-12, wherein the acetyl-leucine is acetyl-DL-leucine.

14. The use according to any of claims 1-12 wherein the acetyl-leucine has an enantiomeric excess of the L-enantiomer or the D-enantiomer.

15. The use according to any of claims 1-4, wherein the acetyl-leucine is to be administered to the subject in need thereof at a therapeutically effect amount of from 0.5 g to about 15 g per day, from about 1 g to about 10 g per day, from about 1.5 g to about 7 g per day, from about 4 g to about 6 g per day, or from about 4 g to about 5 g per day.

16. The use according to any of claims 5-12, wherein the therapeutically effective amount of acetyl-leucine is of from about 0.5 g to about 15 g per day, from about 1 g to about 10 g per day, from about 1.5 g to about 7 g per day, from about 4 g to about 6 g per day, or from about 4 g to about 5 g per day.

17. The use according to claim 1, for reducing the severity of a neurodegenerative disease or reducing the severity of or eliminating one or more existing symptoms associated with a neurodegenerative disease in a subject in need thereof.

18. The use according to claim 1, for providing neuroprotection in a subject having, suspected of having, or at risk of having a neurodegenerative disease, wherein a therepeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.