TREATMENT OF DISEASES ASSOCIATED WITH HEPATIC STELLATE CELL ACTIVATION USING AMMONIA-LOWERING THERAPIES

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/083,814, filed on November 24, 2014, which is herein expressly incorporated by reference in its entirety.

BACKGROUND

Field

[0002] The present application relates to the fields of pharmaceutical chemistry, biochemistry and medicine. One aspect relates to the treatment and/or prevention of diseases associated with hepatic stellate cell (HSC) activation using ammonia-lowering therapies.

Description of the Related Art

[0003] Hepatic stellate cells (HSCs) are pericytes found in the perisinusoidal space of the liver. Within the liver, stellate cells play an important role in maintaining architectural integrity of the liver and are involved in fibrosis and liver cancer development. In normal liver, HSCs are in a quiescent state. When the liver is damaged, HSCs can change into an activated state. The activated stellate cell is characterized by proliferation, contractility and chemotaxis. Various diseases can result from the activation of HSCs, for example, non-alcoholic fatty liver disease (NAFLD), fibrotic conditions, and liver cancer.

[0004] Various prevention, treatment and management strategies for diseases associated with the activation of HSCs are currently available depending upon the severity of the symptoms. There is a need for additional therapies for treating or preventing those diseases.

SUMMARY

[0005] Some embodiments disclosed herein provides a method of treating a disease associated with hepatic stellate cell (HSC) activation, wherein the method

CLAIMS

1. Use of an ammonia-lowering agent in the manufacture of a medicament for the treatment of a disease associated with hepatic stellate cell (HSC) activation.

2. Use of an ammonia-lowering agent in the manufacture of a medicament for the delay of the onset or progression of a disease associated with hepatic stellate cell (HSC) activation.

3. The use of claim 1 or 2, wherein the ammonia-lowering agent comprises a magnesium phosphate product (MGP), glycerol phenylbutyrate (GPB), sodium phenylacetate, sodium phenylbutyrate (NaPBA), glutamine, sodium benzoate, L-arabinose, a laxative, an antibiotic, ornithine in combination with at least one of phenylacetate and phenylbutyrate, or any combination thereof.

4. The use of claim 1 or 2, wherein the ammonia-lowering agent comprises ornithine in combination with at least one of phenylacetate and phenylbutyrate.

5. The use of claim 4, wherein the ammonia-lowering agent comprises separate pharmaceutically acceptable salts of the ornithine and at least one of phenylacetate and phenylbutyrate.

6. The use of claim 4 or 5, wherein the ammonia-lowering agent comprises a sodium phenylacetate or sodium phenylbutyrate.

7. The use of claim 4, wherein the ammonia-lowering agent comprises a free monomeric amino acid or physiologically acceptable salt of ornithine.

8. The use of claim 4, wherein the ammonia-lowering agent comprises ornithine phenylacetate.

9. The use of any one of claims 1-8, wherein the medicament is for oral, intravenous, intraperitoneal, intragastric, or intravascular administration.

10. The use of any one of claims 1-8, wherein the medicament is for intravenous administration.

11. The use of any one of claims 1-8, wherein the medicament is for oral administration.

12. The use of any one of claims 1-11, wherein the disease associated with HSC activation is non-alcoholic fatty liver disease (NAFLD).

13. The use of claim 12, wherein the NAFLD is non-alcoholic steatohepatitis (NASH).

14. The use of claim 12, wherein the NAFLD is steatosis.

15. The use of any one of claims 1-11, wherein the disease associated with HSC activation is liver cancer.

16. The use of any one of claims 1-11, wherein the disease associated with HSC activation is a fibrotic condition.

17. The use of claim 16, wherein the fibrotic condition is liver fibrosis.

18. Use of an ammonia-lowering agent in the manufacture of a medicament for the prevention of non-alcoholic fatty liver disease (NAFLD).

19. The use of claim 18, wherein the NAFLD is non-alcoholic steatohepatitis (NASH).

20. The use of claim 18, wherein the NAFLD is steatosis.

21. The use of any one of claims 18-20, wherein the ammonia-lowering agent comprises a magnesium phosphate product (MGP), glycerol phenylbutyrate (GPB), sodium phenylacetate, sodium phenylbutyrate (NaPBA), glutamine, sodium benzoate, L-arabinose, a laxative, an antibiotic, ornithine in combination with at least one of phenylacetate and phenylbutyrate, or any combination thereof.

22. The use of any one of claims 18-20, wherein the ammonia-lowering agent comprises ornithine in combination with at least one of phenylacetate and phenylbutyrate.

23. The use of claim 22, wherein the ammonia-lowering agent comprises separate pharmaceutically acceptable salts of the ornithine and at least one of phenylacetate and phenylbutyrate.

24. The use of claim 22 or 23, wherein the ammonia-lowering agent comprises a sodium phenylacetate or sodium phenylbutyrate.

25. The use of claim 22, wherein the ammonia-lowering agent comprises a free monomeric amino acid or physiologically acceptable salt of ornithine.

26. The use of claim 22, wherein the ammonia-lowering agent comprises ornithine phenylacetate.

27. The use of any one of claims 18-26, wherein the medicament is for oral, intravenous, intraperitoneal, intragastric, or intravascular administration.

28. The use of any one of claims 18-26, wherein the medicament is for intravenous administration.

29. The use of any one of claims 18-26, wherein the medicament is for oral administration.