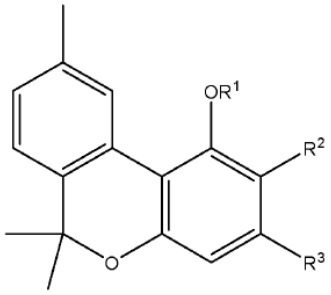
[0014] Cannabinoids, and derivatives thereof, have several properties with therapeutic potential. Activation or blocking of CB1 and/or CB2 receptors with a cannabinoid can regulate downstream signaling and metabolic pathways and subsequently influence synaptic transmission, including transmission of pain and other sensory signals in the periphery, immune response, and inflammation. Thus, there is an interest in the use of natural or synthetic cannabinoids for therapeutic purposes. However, despite anecdotal reports of cannabinoid therapeutic effects, many cannabinoids and their derivatives have been demonstrated to exhibit no detectable neuroprotective effect at physiological concentrations. Moreover, some cannabinoids and their derivatives have been shown to contribute to excitotoxicity at physiological concentrations.

SUMMARY

[0015] Described herein are neuroprotective compositions and formulations, and methods of their making and use. A neuroprotective composition, or a formulation containing a neuroprotective composition, can be contacted with a neuron, thereby providing a neuroprotective effect. In certain examples, the contacting is performed by administering the neuroprotective composition, or a formulation containing the composition, to a subject in need thereof. The neuroprotective compositions, formulations, and related methods are useful in treating a wide variety of neurodegenerative diseases. In certain examples, neuroprotective compositions are provided for use in inducing a neuroprotective effect in retinal neurons. For example, a neuroprotective composition can be locally or systemically administered to a subject to induce a neuroprotective effect in retinal neurons, e.g., to treat an optical neurodegenerative disease such as glaucoma or inhibit neurodegeneration associated with diabetic retinopathy, AMD, and/or retinitis pigmentosa.

[0015a] In one aspect, the present disclosure refers to a use of a composition comprising a neuroprotective compound an amount sufficient to inhibit neurodegeneration in the manufacture of a medicament for protecting a neuron from neurodegeneration, wherein the composition is to be contacted with the neuron, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

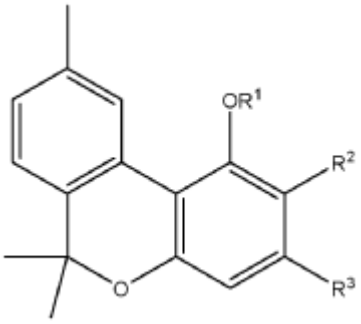
R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof.

[0015b] In another aspect, the present disclosure refers to a use of a composition comprising a neuroprotective compound as described herein, in the manufacture of a medicament for the treatment of neurodegeneration in a subject in need thereof.

[0015c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a neuroprotective compound in an eye drop formulation, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*- C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof.

[0015d] In another aspect, the present disclosure refers to the composition comprising neuroprotective compound as described herein for use in therapy.

[0016] In one example, the present disclosure provides a method of protecting a neuron from neurodegeneration, the method comprising contacting the neuron with a composition comprising cannabinol, or a derivative thereof, in an amount sufficient to inhibit neurodegeneration. In some examples, the contacting is *in vitro*. In some examples, the contacting is *in vivo*. In some examples, the contacting comprises administering the composition to a subject in need thereof. In some examples, the neuron is a retinal neuron (e.g., retinal ganglion).

[0017] In some examples, the contacting comprises topically administering the composition to a subject in need thereof. For example, administering the composition to a

subject suffering from neurodegeneration, e.g., neurodegeneration of the eye. In some cases, the contacting comprises administering the composition to a subject suffering from a neurodegenerative disease, e.g., a neurodegenerative disease of the eye. In some cases, the contacting comprises administering the composition to a subject suffering from glaucoma. In some cases, the contacting comprises administering the composition to a subject diagnosed with glaucoma. In some examples, the method comprises simultaneously or sequentially administering an additional active agent for treatment of glaucoma.

[0018] In some cases, the contacting comprises administering the composition to a subject suffering from AMD. In some cases, the contacting comprises administering the composition to a subject diagnosed with AMD. In some examples, the method comprises simultaneously or sequentially administering an additional active agent for treatment of AMD.

[0019] In some cases, the contacting comprises administering the composition to a subject suffering from diabetic retinopathy. In some cases, the contacting comprises administering the composition to a subject diagnosed with diabetic retinopathy. In some examples, the method comprises simultaneously or sequentially administering an additional active agent for treatment of diabetic retinopathy.

[0020] In some cases, the contacting comprises administering the composition to a subject suffering from retinitis pigmentosa. In some cases, the contacting comprises administering the composition to a subject diagnosed with retinitis pigmentosa. In some examples, the method comprises simultaneously or sequentially administering an additional active agent for treatment of retinitis pigmentosa.

[0021] In some examples, the amount sufficient to inhibit neurodegeneration is an amount sufficient to reduce an amount or rate of apoptosis of a population of neurons contacted with the composition. In some examples, the neuron is subject to elevated hydrostatic pressure and the method comprises contacting the neuron with the composition comprising cannabinol, or a derivative thereof, in an amount sufficient to reduce pressure-induced neurodegeneration.

[0022] In some examples, the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 0.15 μM to less than about 15 μM of cannabinol (or a derivative thereof, such as cannabinolic acid, or a prodrug thereof) in contact with the target neuron, target neuronal population, or in the ocular tissues of the eye. In some examples, the amount sufficient to inhibit neurodegeneration is an amount that results in

a concentration of greater than about 0.5 μM and less than 15 μM of cannabinol in contact with the target neuron, target neuronal population, or in the ocular tissues of the eye.

[0023] In some examples, the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 0.5 μM to less than 15 μM of cannabinol (or a derivative thereof, such as cannabinolic acid, or a prodrug thereof), preferably from greater than about 0.5 μM to less than 12 μM of cannabinol (or a derivative thereof, such as cannabinolic acid, or a prodrug thereof) in contact with the target neuron, target neuronal population, or in the ocular tissues of the eye. In some examples, the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 1.5 μM to 10 μM of cannabinol (or a derivative thereof, such as cannabinolic acid, or a prodrug thereof) in contact with the target neuron, target neuronal population, or in the ocular tissues of the eye.

[0024] In some examples, the cannabinol is provided in an extended release formulation. In some examples, the formulation comprises: a) a delivery carrier comprising a cellulosic polymer and an anionic polysaccharide; and b) nanoparticles comprising an amphiphilic non-ionizable block copolymer and cannabinol, wherein the formulation has a gel point of about 30 °C to about 37 °C.

[0025] In some examples, the contacting comprises systemically administering the composition comprising cannabinol or a prodrug thereof, or a derivative thereof such as cannabinolic acid or a prodrug thereof. In some examples, the systemic administration comprises intravenous injection. In some examples, the systemic administration comprises oral administration. In some examples, the systemic administration comprises transdermal administration.

[0026] In some examples, the contacting comprises local administration of the composition comprising cannabinol or a prodrug thereof, or a derivative thereof such as cannabinolic acid or a prodrug thereof. In some cases, the contacting comprises
administering the composition comprising cannabinol or a prodrug thereof, or a derivative thereof such as cannabinolic acid or a prodrug thereof, directly to the eye. For example, the contacting can comprise administering the composition comprising cannabinol or a prodrug thereof, or a derivative thereof such as cannabinolic acid or a prodrug thereof, onto the eye (e.g., as an eyedrop such as in the form of a microemulsion eyedrop, or an eyegel). As another example, the contacting can comprise administering the composition comprising

cannabinol or a prodrug thereof, or a derivative thereof such as cannabinolic acid or a prodrug thereof, directly into the eye (e.g., via intravitreal injection or pump).

[0027] In another example, described herein is a composition for treatment of neurodegeneration in a subject comprising cannabinol, or a derivative thereof. In some examples, the composition is a pharmaceutical formulation suitable to achieve a neuroprotective dose of cannabinol, or a derivative thereof. In some examples, the composition is formulated for administration to the eye. In some examples, the composition is formulated to achieve a concentration of from about 0.15 μM to less than about 15 μM cannabinol, or derivative thereof, in the ocular tissues of the eye and/or in contact with retinal ganglions.

[0028] In another example, described herein is a use of a composition comprising cannabinol, or a derivative thereof, for treatment of neurodegeneration in a subject, such as hydrostatic pressure induced neurodegeneration, preferably according to one or more of the foregoing examples, examples, cases, or examples, with a composition described herein, or according to a method described herein.

INCORPORATION BY REFERENCE

[0029] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

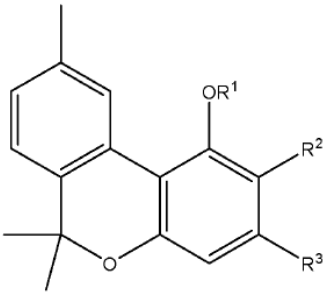
[0030] Fig. 1 illustrates in vitro neuroprotection of differentiated 661W retinal ganglion precursor-like cells cultured under atmospheric pressure by contacting the cells with CBD, CBDA, CBC, CBG, CBGA, CBN, CBND, Δ^9-THC at 0.5 μM, 1.5 μM and 5 μM respectively for each cannabinoid. Vehicle Control (VC) contained 0.15% ethanol. Data presented as Cell Death (%) vs Vehicle Control (taken as 0%). Treatment conditions: 72 hours at concentrations of 0.5, 1.5 and 5 μM for different Cannabinoids, or vehicle control (VC).

[0031] Fig. 2 illustrates an absence of significant neuroprotection of differentiated 661W cells when cultured in a pressurized chamber with elevated hydrostatic pressure of approximately 20 to 40 mm Hg by contacting cells with CBD, CBDA, Δ^9-THC, CBGA, or

CLAIMS

What is claimed is:

1. Use of a composition comprising a neuroprotective compound an amount sufficient to inhibit neurodegeneration in the manufacture of a medicament for protecting a neuron from neurodegeneration, wherein the composition is to be contacted with the neuron, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof.

2. The use of claim 1, wherein the composition is to be administered to a subject in need thereof.

3. The use of claim 1 or 2, wherein the neuron is a retinal neuron.

4. The use of claim 2 or 3, wherein the composition is to be administered to a subject in need thereof and the subject is suffering from a neurodegenerative disease.

5. The use of claim 4, wherein neurodegenerative disease is a neurodegenerative disease affecting the eye, preferably wherein the neurodegenerative disease is selected from the group consisting of glaucoma, age-related macular degeneration (AMD) retinitis pigmentosa, and diabetic retinopathy.

6. The use of claim 4, wherein neurodegenerative disease is glaucoma.

7. The use of claim 6, wherein the composition is to be administered simultaneously or sequentially with an additional active agent for treatment of glaucoma.

8. The use of any one of claims 1 to 7, wherein the amount sufficient to inhibit neurodegeneration is an amount sufficient to reduce an amount or rate of apoptosis of a population of neurons contacted with the composition.

9. The use of any one of claims 1 to 8, wherein the neuron is subject to elevated hydrostatic pressure and the neuron is to be contacted with the composition comprising the neuroprotective compound in an amount sufficient to reduce pressure-induced neurodegeneration.

10. The use of any one of claims 1 to 9, wherein the composition comprising the neuroprotective compound is provided in a microemulsion.

11. The use of any one of claims 1 to 9, wherein the composition comprising the neuroprotective compound is provided in an extended release formulation.

12. The use of claim 11, wherein the formulation comprises:

a. a delivery carrier comprising a cellulosic polymer and an anionic polysaccharide; and

b. nanoparticles comprising an amphiphilic non-ionizable block copolymer and the neuroprotective compound,

wherein the formulation has a gel point of about 30 °C to about 37 °C.

13. The use of any one of claims 1 to 12, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 0.15 μM to less than about 15 μM of the neuroprotective compound in contact with the neuron.

14. The use of claim 13, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of greater than about 0.5 μM and less than 15 μM of the neuroprotective compound in contact with the neuron.

15. The use of claim 14, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 0.5 μM to less than 15 μM of the neuroprotective compound, preferably from greater than about 0.5 μM to less than 12 μM of the neuroprotective compound in contact with the neuron.

16. The use of claim 15, wherein the amount sufficient to inhibit neurodegeneration is an amount that results in a concentration of from about 1.5 μM to 10 μM of the neuroprotective compound in contact with the neuron.

17. The use of any one of claims 1 to 16, wherein
the composition comprising the neuroprotective compound is to be administered systemically.

18. The use of claim 17, wherein the systemic administration comprises intravenous injection.

19. The use of any one of claims 1 to 16 wherein the composition comprising the neuroprotective compound is to be administered locally.

20. The use of any one of claims 1 to 16, wherein
the composition comprising the neuroprotective compound is to be administered directly to the eye.

21. The use of claim 20, wherein the neuroprotective compound in an eye drop formulation is to be administered to the eye.

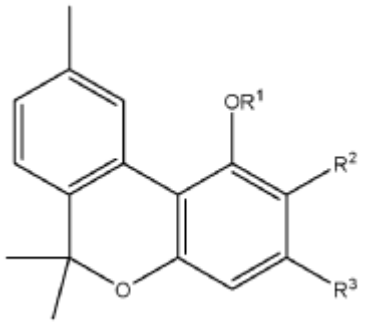
22. The use of claim 21, wherein the eye drop formulation is to be administered weekly, daily, or twice daily.

23. The use of any one of claims 1 to 22, wherein the neuroprotective compound is cannabinol, or cannabinolic acid, or a prodrug thereof.

24. The use of claim 23, wherein the neuroprotective compound is cannabinol.

25. Use of a composition comprising a neuroprotective compound as defined in claim 1, in the manufacture of a medicament for the treatment of neurodegeneration in a subject in need thereof.

26. A pharmaceutical composition comprising a neuroprotective compound in an eye drop formulation, wherein the neuroprotective compound comprises a compound of Formula I:



I , wherein

R^1 is H, R^2 is COOH, and R^3 is *n*- C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is CH_3, R^2 is H, and R^3 is *n*-C_5H_{11};

R^1 is H, R^2 is H, and R^3 is *n*-C_4H_9;

R^1 is H, R^2 is H, and R^3 is *n*-C_3H_7;

R^1 is H, R^2 is H, and R^3 is C_2H_5; or

R^1 is H, R^2 is H, and R^3 is CH_3,

or a derivative thereof.

27. The pharmaceutical composition of claim 26, wherein the neuroprotective compound is present at a concentration of from 0.1% w/w to 0.5% w/w.

28. The pharmaceutical composition of claim 26 or 27, wherein the neuroprotective compound is cannabinol, or cannabinolic acid.

29. The pharmaceutical composition of claim 26, 27, or 28, wherein the neuroprotective compound is cannabinol.

30. The pharmaceutical composition of any one of claims 26 to 29, wherein the neuroprotective compound is in an amount sufficient to achieve a concentration of from about 0.15 μM to less than about 15 μM of the neuroprotective compound in contact with a target neuron.

31. The pharmaceutical composition of any one of claims 26 to 30, wherein the eye drop formulation is a microemulsion, or a hydrogel formulation.

32. The pharmaceutical composition of claim 31, wherein the eye drop formulation is a hydrogel formulation comprising: a) a delivery carrier comprising a cellulosic polymer and an anionic polysaccharide; and b) nanoparticles comprising an amphiphilic non-ionizable block copolymer and the neuroprotective compound, wherein the formulation has a gel point of about 30 °C to about 37 °C.

33. The composition comprising neuroprotective compound of claim 1 for use in therapy.