Glutathione Trisulfide (GSSSG) in Neuroprotection

CLAIM OF PRIORITY

This application claims the benefit of U.S. Provisional Patent Application Serial No. 63/023,686, filed on May 12, 2020. The entire contents of the foregoing are hereby incorporated by reference.

TECHNICAL FIELD

Described herein is the use of glutathione trisulfide (GSSSG) in neuroprotection, e.g., in neurodegenerative diseases and to reduce the risk of ischemic injury. The methods can be used, e.g., to reduce risk of injury to brain, spinal cord, and peripheral nerves from ischemia or low blood flow states possibly caused by surgery, trauma, and other conditions that decrease/impair blood flow and or oxygen delivery to the nervous system.

BACKGROUND

Delayed paraplegia is a devastating complication of ischemic spinal cord injury (SCI), which can occur after thoracic and/or abdominal aortic surgery and trauma to the spinal cord. While the incidence of ischemic SCI is reported to be around 3%, more than 80% present with delayed onset of symptoms (Ullery et al., 2011). Although mechanisms of delayed paraplegia are incompletely understood, studies suggest critical roles of motor neuron apoptosis (Kakinohana et al., 2011) and recruitment of microglia and bone marrow-derived macrophages (BMDM) in ischemic stroke(Denes et al., 2008) and SCI (Bell et al., 2013; Donnelly et al., 2011; Kigerl et al., 2007).

SUMMARY

Provided herein are methods for the treatment, or reduction of risk, of a disorder associated with neurodegeneration in a subject. The methods include administering a therapeutically or prophylactically effective amount of a composition prepared using crystals of Glutathione Trisulfide (GSSSG) to a subject in need thereof. In some examples, the methods include comprising preparing the composition comprising GSSSG by dissolving a crystalline form of GSSSG in saline at pH 3-6. Also provided

are compositions comprising GSSSG for use in a method of treatment, or reduction of risk, of a disorder associated with neurodegeneration in a subject, e.g., compositions prepared by dissolving a crystalline form of GSSSG in saline at pH 3-6. .

In some examples, the disorder is post-ischemic neuronal death.

In some examples, the disorder is a chronic cerebral degenerative disease, e.g., multi-infarct dementia, Alzheimer's disease, Parkinson's disease, or Lewy body dementia.

In some examples, the methods include administering an effective amount of a composition comprising GSSSG within a few minutes to hours after a traumatic injury occurs.

In some examples, the methods include administering an effective amount of a composition comprising GSSSG before a scheduled thoracic and/or abdominal aortic surgical procedure.

In some examples, the methods include administering an effective amount of a composition comprising GSSSG hours to days before a scheduled thoracic and/or abdominal aortic surgical procedure.

In some examples, the methods include administering an effective amount of a composition comprising GSSSG 2-24 hours, and/or 1, 2, 3, 4, 5, 6, and/or7 days before the scheduled thoracic and/or abdominal aortic surgical procedure.

In one aspect, the present disclosure provides use of a composition comprising Glutathione Trisulfide (GSSSG) in the manufacture of a medicament for the treatment, or reduction of risk, of a disorder associated with neurodegeneration in a subject, wherein a therapeutically or prophylactically effective amount of the composition is to be administered before a scheduled thoracic and/or abdominal aortic surgical procedure to a subject in need thereof, wherein the disorder is post-ischemic neuronal death.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting.

All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

CLAIMS

1. Use of a composition comprising Glutathione Trisulfide (GSSSG) in the manufacture of a medicament for the treatment, or reduction of risk, of a disorder associated with neurodegeneration in a subject, wherein a therapeutically or prophylactically effective amount of the composition is to be administered before a scheduled thoracic and/or abdominal aortic surgical procedure to a subject in need thereof, wherein the disorder is post-ischemic neuronal death.

2. The use of claim 1, wherein the composition comprising GSSSG is prepared by dissolving a crystalline form of GSSSG in saline at pH 3-6.

3. The use of claim 1, wherein an effective amount of the composition comprising GSSSG is to be administered hours to days before a scheduled thoracic and/or abdominal aortic surgical procedure.

4. The use of claim 3, wherein an effective amount of the composition comprising GSSSG is to be administered 2-24 hours, and/or 1, 2, 3, 4, 5, 6, and/or 7 days before the scheduled thoracic and/or abdominal aortic surgical procedure.