Washington University in St. Louis
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NMDA RECEPTOR MODULATOR FOR NEUROPROTECTION AFTER A STROKE

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Disease indication – neuroprotection in stroke/ischemia with potential for treating other neurodegenerative diseases

Drug format – neurosteroid

Drug class – drug repurposing (25-hydroxycholesterol)

Research stage and Preliminary data:

In vitro – The inventors demonstrated the neuroprotective effects of 25-hydroxycholesterol (25-HC) in a neuronal culture model of oxygen-glucose deprivation. In these studies, 25-HC was able to rescue NMDA receptor-dependent cell death mediated by 24S-hydroxycholesterol (24S-HC, a molecule that exacerbates NMDA receptor-dependent excitotoxicity).

Target – NMDA Receptor (N-methyl-D-aspartate receptor)

Background:

Ischemic stroke causes a bioenergetics failure which leads to neuronal damage from excitotoxicity. 24S-HC is a major brain cholesterol metabolite that positively modulates NMDA activity. In vitro stroke models have shown that 24S-HC exacerbates excitotoxicity thereby reducing neuronal survival. Although it is known that NMDA receptors participate in ischemia-induced neuronal death, therapeutic strategies which directly block the NMDA receptor have been difficult to develop due to undesired side effects. Targeting molecules such as 24S-HC (an endogenous positive allosteric modulator of NMDA receptor function) may offer a strategy with fewer downsides.

Keywords – stroke, neuroprotection, ischemia, NMDA receptor, neurosteroid

Mode of action:

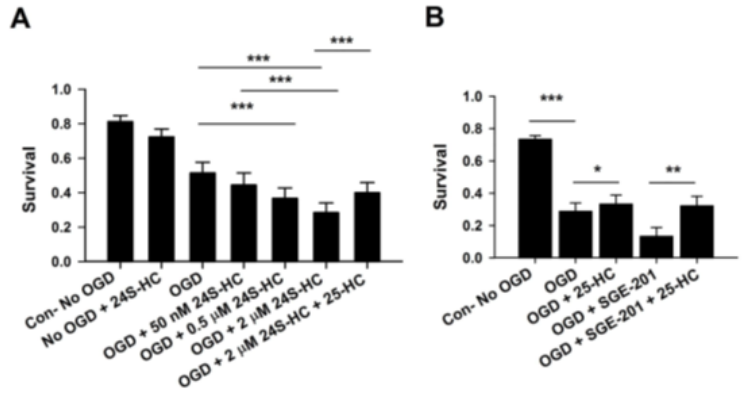
The minor brain cholesterol metabolite 25-HC antagonizes the effects of 24S-HC. This protects neuronal cells from death. These effects are seen even when 25-HC is administered after the ischemic insult, indicating that this strategy could offer a treatment to rescue cells from damage post stroke. Because these effects include a component that is independent of NMDA receptors, the receptors maintain their basal activity. This potentially avoids the deleterious side effects of NMDA receptor antagonists.

Competitive edge:

- **Post-stroke treatment –** the neuroprotective effects of 25-HC administered after the ischemic insult is similar to the effect when 25-HC is administered before the insult
- **Potential for fewer side effects:**

- does not block directly block NMDA receptor
- mechanism for 25-HC protects against excitotoxicity without altering basal NMDA receptor function, lowering the risk of undesired side effects seen in previous NMDA receptor antagonists

Patent application - 25-hydroxycholesterol and methods of use thereof (PCT Publication No. WO2017189561)



Damage from oxygen-glucose deprivation (OGD) is concentration dependent and is partially rescued by 25-HC. *(A) Survival was compared between control, OGD, OGD+50 nM 24S-HC, OGD+0.5 µM 24S-HC, OGD+2 µM24S-HC, and OGD+2 µM 24S-HC+10 µM25-HC. Cells treated with OGD and 24S-HC at 0.5 µM and 2 µMshowed significantly poorer survival compared to those treated with OGD alone. Application of 25-HC partially prevented OGD-induced cell death exacerbated by 2 µM24S-HC. (n = 11 cultures for each group; one-way repeated measures ANOVA with Bonferroni's post hoc test, *P < 0.05; **P < 0.01; ***P<0.001). (B) 25-HC not only partially rescued OGD-induced cell death following SGE-201 application, but also protected against OGD-induced cell death in the absence of 24S-HC analogue application (n = 8 cultures for each group; one-way repeated measures ANOVA with Bonferroni's post hoc test, *P < 0.05; **P < 0.01; ***P < 0.001).*

Publications

- Sun, M. Y., Taylor, A., Zorumski, C. F., & Mennerick, S. (2017). 24S-hydroxycholesterol and 25-hydroxycholesterol differentially impact hippocampal neuronal survival following oxygen-glucose deprivation. *PloS one*, 12(3), e0174416.

Web Links – Mennerick Lab