The Neuroprotective Effects of Metformin: Insights from Rodent Cardiac Arrest and in Vitro Ischemia-reperfusion of Neurons and Astrocytes

Presented During:
Oral Abstract Session - AUA
Thursday, May 13, 2021: 3:21 PM - 3:29 PM

Oral Abstract Session - SOCCA
Friday, May 14, 2021: 2:35 PM - 2:45 PM

Poster Session
Saturday, May 15, 2021: 11:00 AM - 5:45 PM

Submission Number:
765

Reference(s):

Session Type:
Abstract Submission

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Our results suggest that metformin improves survival and cell viability outcomes in both in vivo and in vitro.

### Conclusion:

Metformin significantly improved the cell viability of HT-22 neurons after 6 h of OGD and 20 h of reperfusion in a single-culture of neurons (mouse cell line HT-22) and astrocytes (mouse cell line C8-D1A).

### Methods:

Adult male Sprague–Dawley rats experienced 10 min asphyxial cardiac arrest (CA) followed by resuscitation and received intravenously either metformin (100 mg/Kg in saline; n=16), or vehicle (saline; n=16) immediately following return of spontaneous circulation (ROSC). Survival and modified neurological deficit scores were monitored until 72 h post-ROSC with brains harvested from the surviving rats for histological evaluation. Brain protein carbonyl concentration was determined in both groups as a surrogate marker of reactive oxygen species (ROS) production. Nissl’s staining was performed on the hippocampus CA1 region and dentate gyrus to determine neuronal morphology in both groups. Cell viability assay (WST-8) was assessed after 6 h of oxygen-glucose deprivation (OGD) and 20 h of reperfusion in single-cultures of neurons (mouse cell line HT-22) and astrocytes (mouse cell line C8-D1A).

### Results:

In the rodent model of CA, metformin treatment demonstrated an improved survival at 72 h from 43.8% to 68.8% (p= 0.0692; Kaplan-Meier Analysis with Gehan-Breslow-Wilcoxon test) (Fig.1). Metformin also significantly improved the neurological status at 72 h assessed by modified neurological deficit score when compared with vehicle (p= 0.0103) (Fig. 2). Metformin preserved neuron body integrity in both hippocampal CA1 and dentate gyrus regions observed by Nissl’s staining, when compared with the noticeable neuronal body degeneration in the vehicle group (Fig. 3). Metformin treatment was associated with significantly lower protein carbonyl concentration, revealing significantly lower ROS production versus vehicle group (p= 0.0152). CA resulted in increased ROS production versus sham, determined by protein carbonyl concentration (p= 0.0012). Metformin significantly improved the cell viability of HT-22 neurons after 6 h of OGD and 20 h of reperfusion in a dose dependent manner [10 umol Metformin (p= 0.0425); 50 umol Metformin (p= 0.0336)] (Fig. 5A), but without significant impact on C8-D1A astrocytes (Fig. 5B).
Conclusion:
Our results suggest that metformin improves survival and cell viability outcomes in both in vivo and in vitro models, respectively. Metformin treatment demonstrated increased neurological function and improved brain-cytologic morphology as well as decreased ROS production in our rodent CA model. Furthermore, metformin improved cell viability in single-cultures of HT-22 neurons, with no effect on C8-D1A astrocytes, after OGD and reperfusion, which was observed in a dose dependent fashion. Overall, albeit at a very high dose, metformin could be a potential therapeutic intervention for improving survival and preventing neuronal death after cardiac arrest.

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Fig. 1
Survival Rate up to 72 hrs

Survival Time (hours)
0 10 20 30 40 50 60 70
Percent of Survival (%)
0 20 40 60 80 100
Metformin
Vehicle
68.8%
p=0.0692
43.8%
Fig. 2

Modified Neurological Deficit Score (mNDS) vs. Treatment

Vehicle | Metformin

Fig. 3

CA1

Vehicle | Metformin

DG

Vehicle | Metformin