ORAL PRESENTATIONS • DRUG DISCOVERY AND DEVELOPMENT

[OPD1]

EFFECT OF TRANS-RESVERATROL ON GLUTAMATE CLEARANCE AND VISUAL BEHAVIOR DUE TO EXCITOTOXIC RETINAL INJURY IN RATS

Hann Yih Tee[1], Renu Agarwal[1], Norhafiza Razali[2], Igor Iezhitsa[1], Nafeeza Mohd Ismail[1]

[1]School of Medicine, International Medical University, Kuala Lumpur, Malaysia

[2]Center for Neuroscience Research (NeuRon), Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia

Glutamate excitotoxicity due to excessive synaptic level of glutamate has been implicated in the apoptotic loss of retinal ganglion cells (RGCs) in glaucoma. Glutamate clearance by astrocytes through glutamate transporters, EAAT1 & EAAT2, plays a crucial role in clearing and regulating synaptic glutamate concentration. In this study, we investigated the effect of trans-resveratrol (TR) on glutamate clearance, retinal cell survival and visual behaviour due to glutamate-induced retinal injury in rats.

Sprague-Dawley rats were divided into five groups of 12 animals each. Untreated group did not receive any treatment. Remaining groups received single bilateral intravitreal injections. Vehicle-treated group received PBS (1 mL, 0.1M) while glutamate-treated group received glutamate (1 µL, 50 nM). TR post-treatment group received TR (1 µL, 0.09 µM) 24 hours after glutamate while TR pre-treatment group received same amount of TR 24 hours before glutamate. The visual functions were examined using an Open field and the Mirror chamber test. The rats were sacrificed on day 8 post-treatment, and the retinal expressions of EAAT1, EAAT2 and glutamate concentration were determined using ELISA. The extent of retinal cell survival was determined using H&E staining. The statistical comparison among groups was done using one-way ANOVA followed by post hoc Tukey's test.

It was observed that the glutamate-treated rats had significantly poor visual functions, lower retinal cell density ($p<0.001$) and higher retinal glutamate concentration ($p<0.01$) compared to PBS-treated rats. Pre-treatment with TR protected against glutamate-induced changes in retinal cell density ($p<0.001$ versus glutamate-treated group). It caused significantly higher retinal expression of EAAT1 ($p<0.05$) and EAAT2 ($p<0.05$) and lower retinal glutamate concentration ($p<0.01$) compared to glutamate-treated rats. These effects of TR were associated with preservation of visual functions. Similar effects were not observed in TR post-treatment group.

In conclusion, TR pre-treatment protects against glutamate-induced retinal excitotoxicity by increasing glutamate clearance in rats.

[OPD2]

EFFECT OF TOCOTRIENOL-RICH FRACTION ON VISUAL BEHAVIOUR AND RETINAL CELL APOPTOSIS IN RATS WITH STREPTOZOTOCIN-INDUCED DIABETIC RETINOPATHY

You Goh[1], Abdul Nasir Nurul Alimah[2], Renu Agarwal[1], Mohd Ismail Nafeeza[1], Heethal Jaiprakas[1]

[1]School of Medicine, International Medical University, 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

[2]Centre for Neuroscience Research (NeuRon), Faculty of Medicine, Universiti Teknologi MARA Jalan Hospital, Sungai Buloh, 47000 Selangor, Malaysia

Hyperglycaemia-induced oxidative stress is a recognised underlying pathophysiology in the generation of retinal cell apoptosis associated with diabetic retinopathy. Therefore, our study was based on the following research question: Does orally administered tocotrienol-rich fraction (TRF), a potent antioxidant, protect against loss of visual behaviour and retinal cell apoptosis in rats with streptozotocin (STZ)-induced diabetic retinopathy?

Sprague-Dawley rats were divided into 3 groups: normal rats treated with vehicle (N), diabetic group treated with vehicle (DV), and diabetic group treated with TRF (DT). Diabetes was induced by intraperitoneal STZ injection. After 12 weeks of treatment, the general behaviour of rats was assessed using the open field test, while visual behaviour was evaluated in a dual-chamber place preference apparatus with a mirror. Subsequently, the rats were euthanised and retinas were isolated to estimate the expression of pro- (caspase-3, Bax) and anti-apoptotic (Bcl-2) markers using ELISA.

We observed significant upregulation of pro-apoptotic proteins and downregulation of anti-apoptotic proteins in DV ($p<0.05$) compared to N and DT. The expression of the same parameters in DT was comparable to that in N. Additionally, the Bax/Bcl-2 ratios were 1.43, 5.47 and 0.79 for N, DV and DT groups, respectively. In the open field test, DV demonstrated significantly lower overall exploratory and locomotor activity and more anxiety-related behaviour than N. The behavioural pattern of DT was the opposite in all tested signs compared to DV and was comparable with N. In the visual chambers test, N and DT spent more time in the blank chamber than the mirror chamber, while DV displayed minimal chamber preference.

In conclusion, oral TRF treatment protects against diabetes-induced increase in the expression of pro-apoptotic and reduction in anti-apoptotic proteins in rat retinas. It also preserves against diabetes-induced impairment of visual behaviour of rats. These effects of TRF were evident despite persistent hyperglycaemia.