Effect of insulin on neuroinflammatory response and oxidative stress induced by a blocker of Kv1.3 channel

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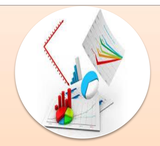
Voltage-dependent potassium channels (Kv1.3), play key role in a wide variety of physiological processes, including immunity, metabolism and the stabilization of the resting potential. In brain, activation of insulin receptor is able to induce current suppression coupled to tyrosine phosphorylation of Kv1.3 channel. Moreover, insulin can reduce the production of free radicals and attenuate the inflammatory response. The Kv1.3 channel blockers, such as neurotoxins isolated from scorpion venom, are able to alter neuronal excitability leading to neurological disorders accompanied by inflammatory response.

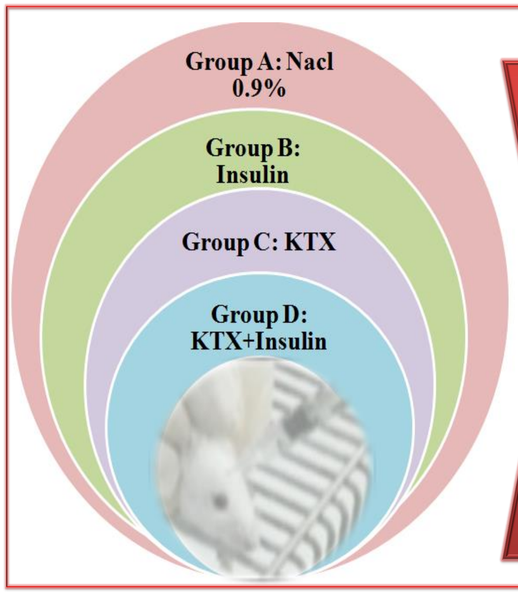
The aim of this study is to evaluate the neuroprotective effect of insulin injected by intra-cerebro-ventricular (i.c.v.) route on neuro-inflammatory response and oxidative stress induced by kaliotoxin (KTX) a blocker of Kv1.3 channel.

The ability of insulin to reduce the brain injuries, inflammatory response and oxidative stress biomarkers induced by KTX were assessed in NMRI mice at 24 h after co-injection of insulin and neurotoxin active on potassium channel.



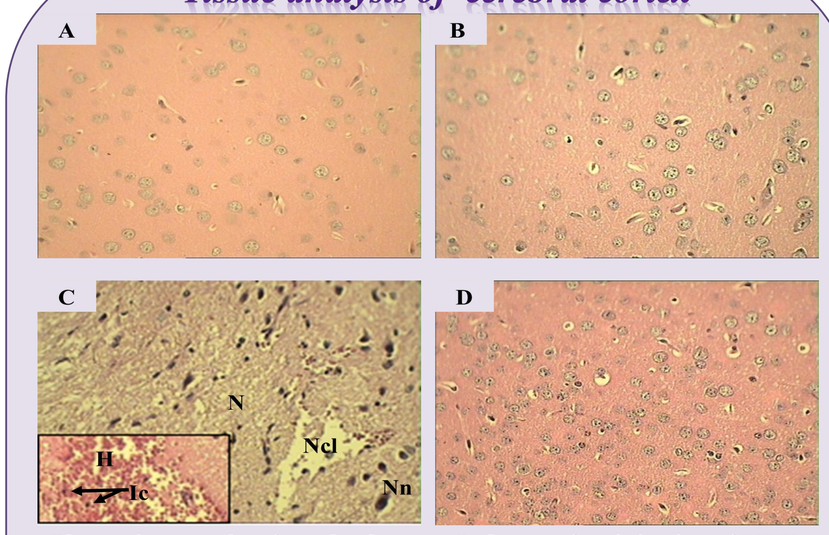
Obtained results revealed that the central administration of insulin prevents cerebral cortex injury, brain edema, cells infiltration and a change in the permeability of the blood–brain barrier induced by KTX. Insulin seems to also reduce significantly the pro-inflammatory cytokines (IL-6, IL-17, TNF-α), MMP-2 and MMP-9 activities and oxidative stress markers (H_2O_2, NO, MDA) in brain homogenates compared to those observed when animals were injected with KTX alone.

Methodology

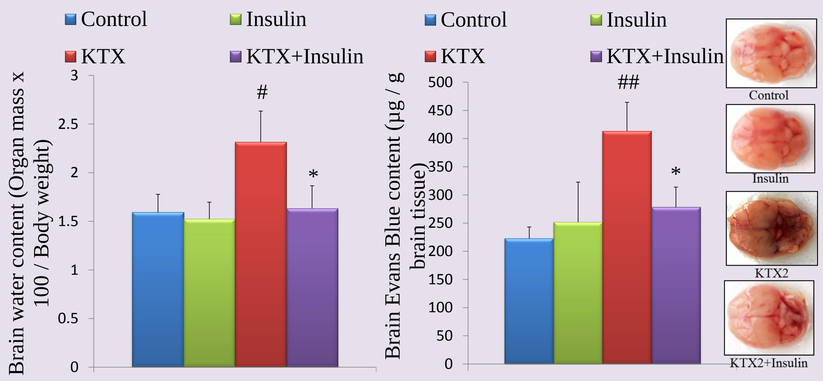


- Animals were sacrificed at 24 h after injection of KTX and insulin by i.c.v. route
- Biomarkers of inflammatory response and stress status were assessed
- Evaluation of blood-brain barrier (BBB) permeability by Evans Blue extravasation.
- Tissue damage in brain tissue and brain edema were evaluated

Tissue analysis of cerebral cortex



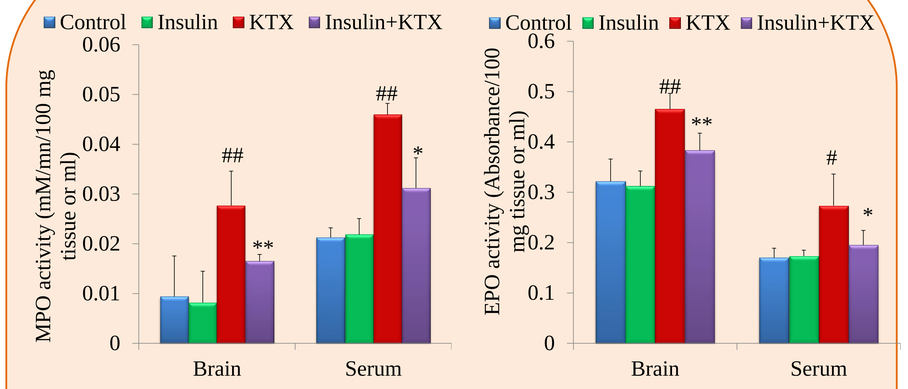
Photomicrographs of cerebral cortex 24 hours after injection of KTX. Hematoxylin-eosin. G×400. (He) Hemorrhage, (Ic) Inflammatory cell infiltrates, (N) Necrosis, (Ncl) Neuronal cell loss, (ND) Neuronal darkness.

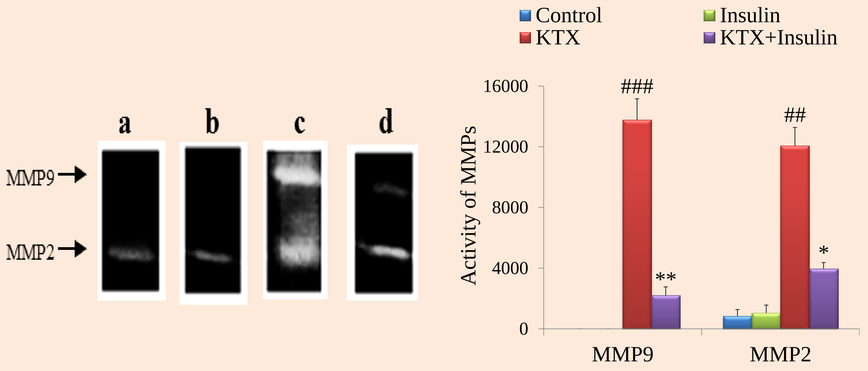


➢injected animals with KTX present sever alterations in cerebral cortex, brain edema and a significant increase of the BBB permeability.

➢The co-injection of KTX with insulin reduces significantly the tissue alterations, attenuates the increased water content in the brain and protected the BBB integrity .

Evaluation of inflammatory response



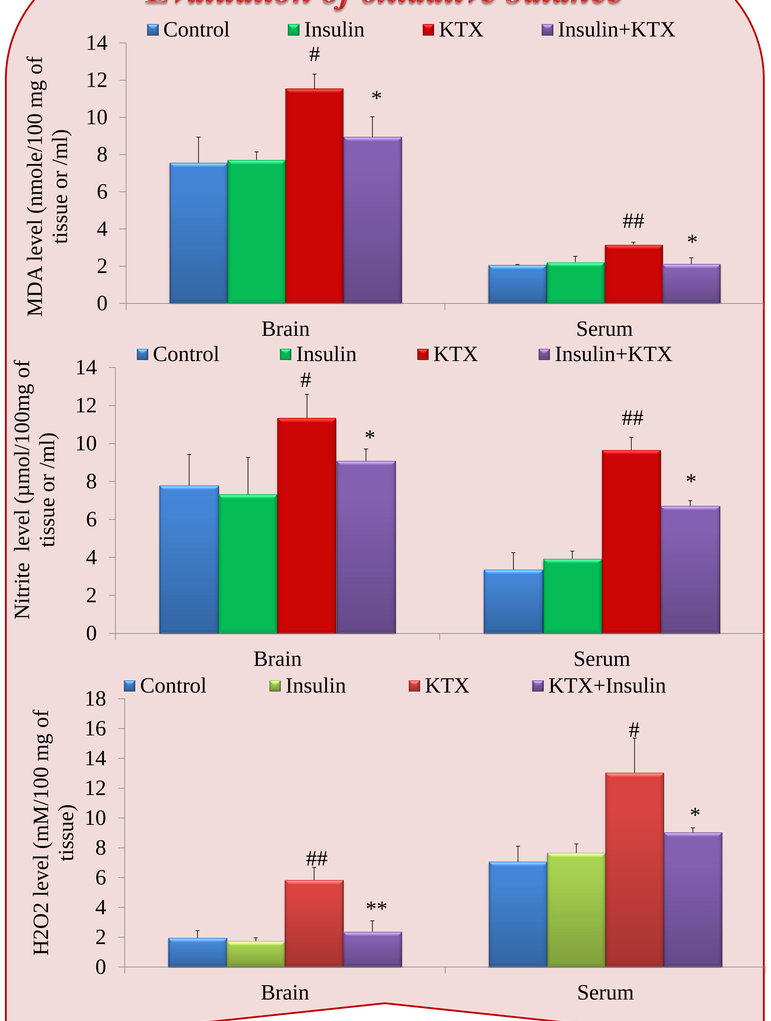


	Control	Insulin	KTX2	KTX2 + Insulin
TNF-α (pg/mL)	811.42 ± 80.81	782.85 ± 28.57	1144.76 ± 43.64 ##	840 ± 40.40 **
IL-6 (pg/mL)	170 ± 75.71	136.42 ± 59.59	632.85 ± 147.14 ##	240.47 ± 84.95*
IL-17 (pg/mL)	527.4 ± 7.91	544.6 ± 6.22	769.53 ± 47.76 ##	629.4 ± 6.22 *

➢injected animals with KTX present significant increase of inflammatory mediators: serum cytokines ,eosinophil peroxidase, myeloperoxidase, MMP-2 and MMP-9 activities.

➢The co-injection of KTX with insulin reduces significantly the biomarkers levels of inflammation.

Evaluation of oxidative balance



➢injected animals with KTX present significant increase of oxidative stress markers (malondialdehyde, nitrite, hydrogen peroxide).

➢The co-injection of KTX awith insulin reduces significantly the biomarkers levels of oxidative stress.

Conclusion:

These results indicate that insulin is able to modulate the activity of potassium channels in brain by modifying their properties, which probably prevent the binding of neurotoxin to its receptor Kv channel and thus reduce the neuro-pathophysiological effects. These data suggest that insulin is not only vital to the brain but it may also exert an influence modulating several brain functions in which Kv1.3 channel are involved. The use of Kv1.3 channel modulators such as KTX or insulin could be potential pharmacological tools that can elucidate or better understand neurological mechanisms in the pathogenesis related to the dysfunction of ion channels such as multiple sclerosis, epilepsy and Alzheimer's diseases.