

Chapter 7:
Summary
and
Conclusion

SUMMARY AND CONCLUSION

The present study was designed to investigate the possible mechanism of STZ-induced decrease in antinociceptive effect of NSAIDs, opioids, cannabinoids and neurosteroids, in the rats.

On the basis of results obtained in the present study, the following salient features have emerged;

STZ-diabetic animals exhibit thermal hyperalgesia and allodynia and mechanical allodynia along with a significant increase in TBARS and nitrite level. The level of antioxidant enzymes i.e SOD, CAT and GSH was significantly reduced in STZ-treated animals.

Treatment with opioids, NSAIDs and Cannabinoids produced antinociceptive effect in a dose dependent manner. However, antinociceptive effect of all these analgesics was significantly reduced in STZ-treated animals.

Chronic administration of NSAIDs, cannabinoid and neurosteroids significantly attenuated the hyperglycemia induced increase in levels of TBARS and nitrite and restored depleted GSH and reduced activity of SOD in tissue, implicating involvement of antioxidant mechanisms via reduced oxidative stress in reversal of analgesic tolerance in diabetic animals.

SHS injection of diabetic animals significantly reduced analgesics effect, when injected in non-diabetic animals, very similar to that observed in diabetic animals. On the other hand, antinociceptive effect of these analgesics was not altered in splenectomised animals.

Administration of dextrometharphan, ketamine (NMDA antagonist) cyclosporine, thalidomide, pentoxifylline (cytokines inhibitor), minocycline (glial cell modulator), L-NAME and aminoguanidine (NOS-inhibitor), significantly attenuated the increase

in nitrite level in diabetic animals and prevented the development and or reversed the existing tolerance to all analgesics drugs used. This beneficial effect was significantly decreased by L-arginine, a donor of NO.

On the basis of results obtained in this study, it may be concluded that hyperglycemia induced multifaceted mechanism such as an increase in oxidative stress, cytokines, and NMDA activation and factor (s) from spleen mononuclear cells, lead to an increase in NO/ONOO- production and the formed ONOO-consequently decrease the antinociceptive effect of analgesics. This study indicates that oxido-nitrosative stress may be the unifying mechanism involved in developments of tolerance to analgesic drugs in diabetic patients.