Chapter 5

Summary and Conclusion

5.1 Summary and conclusion

The important finding was the hyperactivity of the peripheral and central orexinergic system in PTSD. Activation of the orexinergic system significantly correlated with the PTSD-like phenotypes. Further, there was extra-hypothalamic CRF system activation as observed from the up-regulation of CRF-R1 in the amygdala. Sub-chronic treatment with suvorexant counteracted the hyperactivity of orexinergic and serotonergic system and attenuated PTSD-like symptoms in SRS exposed rats. Moreover, the suvorexant-induced anti-PTSD-like effect was comparable to paroxetine. Additionally, suvorexant (10 and 20 mg/kg) attenuated SRS-induced alteration in locomotion and produced a sedative effect with its highest dose (30 mg/kg) in unstressed rats. Thus, targeting the orexinergic system can be a potential treatment strategy for patients with sleep-related disturbance in PTSD, but this must be further validated.

The exposure to SRS prompted cognitive inflexibility and hypoactivity of the cholinergic system. Interestingly, SRS exposure also reduced ACh's biosynthesis and its postsynaptic action by down-regulating ChAT and α-7nAChR expressions. Unlike sertraline, donepezil reduced AChE activity and enhanced ACh, and thereby mitigated cognitive inflexibility. Cognitive flexibility is essential for developing adaptive behaviour and is required for the decision-making ability and coping with fear response during traumatic conditions. Therefore, cholinergic drugs such as donepezil in the treatment protocol may benefit PTSD patients where cognitive inflexibility is the major symptom.

Further, the repeated exposure of SRS caused disparity in mitochondrial dynamics as observed by enhanced fission regulating protein (Drp-1 and Fis-1) and reduced fusion diagnostic thresholds have been lowered for children and adolescents. Furthermore, separate criteria have been added for children age six years or younger with this disorder (Friedman et al., 2011, Kilpatrick et al., 2013).

regulating protein (Opa-1 and Mnf-2) in rats. The modulation in mitochondrial dynamics is mediated by orexin-A dependent activation of mTORC-1 pathway and translation of MTFP-1. There was an increase in Drp-1 and a decrease in Mnf-2 co-localisation intensity in the AMY. The altered mitochondrial dynamics caused fewer mitophagy vacuoles with more swollen and damaged mitochondria. Treatment with suvorexant and rapamycin significantly improved mitochondrial dynamics together with PTSD-like phenotypes in rats. Moreover, the combination of suvorexant and rapamycin synergistically mitigated the mTORC-1 activation and eliminated non-functional mitochondria and promoted mitophagy for final degradation. Therefore, mitochondrial dynamics is an essential factor in the development of PTSD and its treatment.

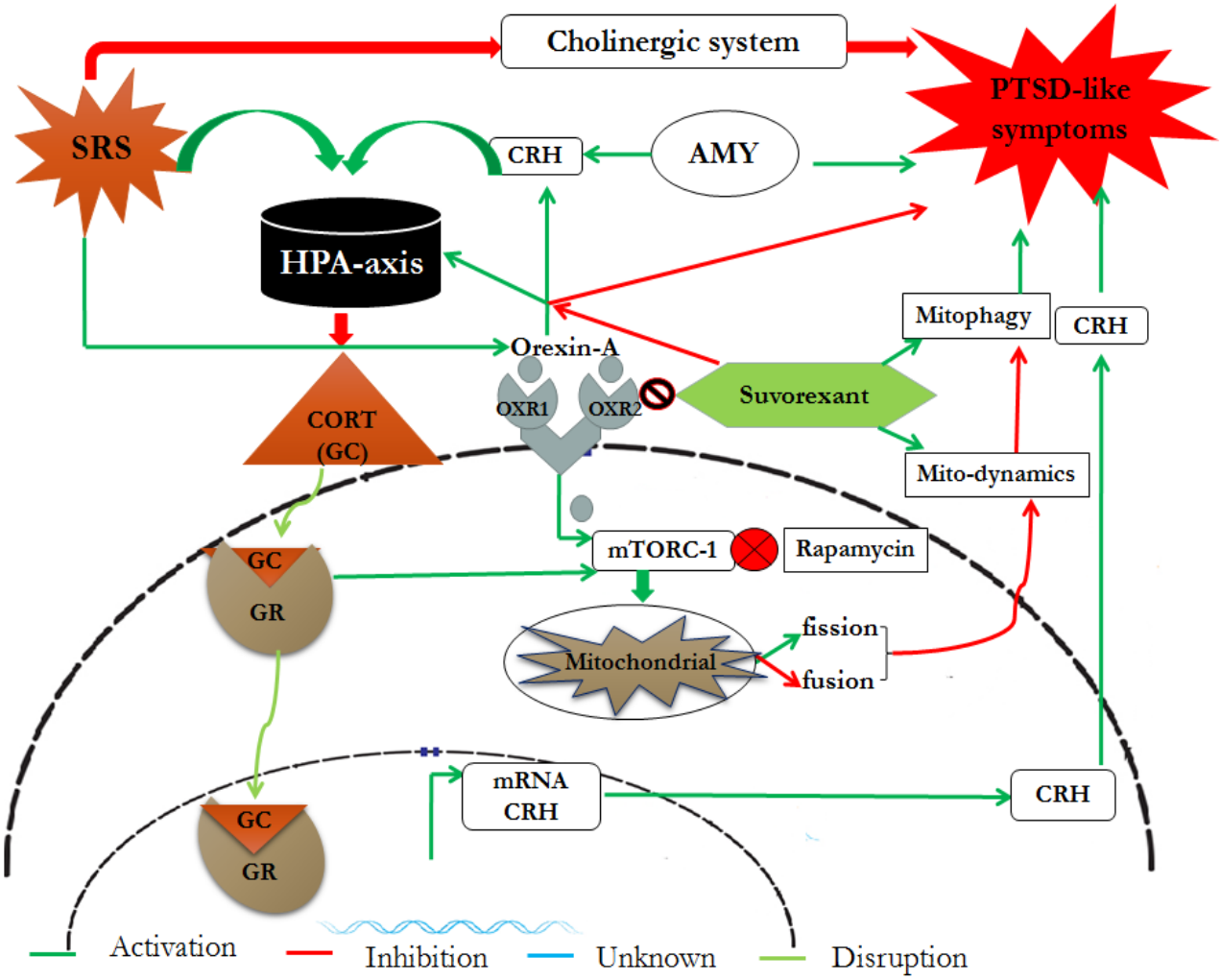

Figure 5.1 Summary and conclusion of the study: green arrow represents activation; however, red arrow denotes inhibition.

Orexin-A regulates both clinically (HPA-axis disruption and serotonergic activation) and experimentally (mitochondrial dysfunction) observed pathology of PTSD. Non-selective antagonism of orexin-A receptor mitigated PTSD-like symptoms and cognitive inflexibility. It also facilitated mitochondrial dynamics and mitophagy in a rodent model of PTSD. Thus, suvorexant can be a potential candidate for the management of PTSD.

5.2 Important outcomes

- Overall findings implicate hyperactivity of the orexinergic system and disrupt hypothalamic HPA-axis and extra-hypothalamic CRH system in PTSD.
- These effects were significantly attenuated by suvorexant together with PTSD-like symptoms.
- Exposure of SRS caused cognitive inflexibility and hypo-activity of the cholinergic system in PFC and HIP (brain regions for the execution of fear response)
- The use of cholinergic enhancer, i.e., donepezil significantly attenuated the cognitive inflexibility and the acquisition of fear and anxiety-like behaviour.
- Repeated exposure of SRS alters mitochondrial dynamics and this effect was significantly attenuated by suvorexant alone and in the combination rapamycin.
- Suvorexant mitigates activation of mTORC-1 and associated downstream cascade such as MTFP-1 and facilitates mitochondrial mitophagy.