6.0. Summary and Conclusions
6.6. SUMMARY AND CONCLUSIONS

Presynaptic control via histamine $H_3$ receptors (autoreceptors) is an important mechanism of histamine-mediated neurotransmission. The CNS effects of selective ligands of these receptors are currently an area of great interest. While experimental evidence from several studies indicate a variety of central effects following $H_3$ receptor stimulation or blockade and a therapeutic potential for $H_3$ receptor blockers in epilepsy and cognitive function disorders, little is known about the role of these ligands in neuropsychiatric disorders (anxiety, depression and schizophrenia) and cerebral ischemia. There are, however, indicators (both direct and indirect) for the involvement of histamine (HA) in these conditions requiring an effort in this direction and hence our study. Nonetheless, the understanding of underlying mechanisms in the pathogenesis of above-mentioned disorders is incompletely understood and hence attempts have been made to explore novel targets for these conditions. We chose to explore $H_3$ receptor ligands for these conditions as histaminergic neuronal system has now gained the status of a regulatory center for whole brain activity. In addition, a highly localized CNS distribution of $H_3$ receptors with extensive modulatory role is indicative of the vast potential for the ligands of these receptors in various CNS disorders. Further, since oxidative stress (OS) is considered to be an important predisposing factor in the etiology of depression and cerebral ischemia, the study also investigated the effects of these ligands on oxidative stress markers in the rodent brain.

Thus, the present study was planned with the following aims and objectives:

(i) To investigate some selective histamine $H_3$ receptor ligands (thioperamide, a selective antagonist (THP) and R-$(\alpha)$-methyl histamine (RAMH), a selective agonist) in rodent models for anxiety, depression, schizophrenia and cerebral ischemia.

(ii) To probe the involvement of oxidative stress in some of these disorders (depression and cerebral ischemia) and in the action of selective $H_3$ receptor ligands.
Experimental models of anxiety (Vogel's conflict test [VCT] using habitest™ lickometer and elevated plus maze [EPM]), depression (modified forced swimming test [FST]), schizophrenia (bar test, amphetamine-induced locomotor activity [LA], apomorphine-induced climbing) in mice and cerebral ischemia (middle cerebral artery occlusion [MCAO] model of focal ischemia) in rats were used. Locomotor activities were assessed using photoactometer and videopath activity analyzer, wherever required. Effects on cognitive functions and grip strength of the animal was assessed by spontaneous alternation behavior (SAB) in a cross maze and grip strength meter respectively. The biochemical evaluations included estimations of thiobarbituric acid reactive substance (TBARS), reduced glutathione (GSH) and catalase levels in brains of mice following modified FST and in addition to these glutathione -S- transferase (GST), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD) and brain nitrate and nitrite levels in brain following MCAO occlusion in rats.

The findings may be summarized as below:

Anxiety
- No significant effect was observed following THP and RAMH in VCT and EPM in mice.

"Our results suggest a lack of effect on anxiety following HA receptor stimulation or blockade".

Depression
- A dose dependent decrease in immobility time and an increase in swimming time were observed in the modified FST following THP. RAMH was without any effect. None of the two drugs affected the climbing behavior. Fluoxetine produced effects similar to THP.

"THP elicits dose-dependent antidepressant effects in the modified FST. A possible role for serotonergic mechanism in the antidepressant effect of THP is suggested".
Summary and conclusions

- Modified FST produced oxidative stress. Both THP and fluoxetine reversed the reduced GSH and elevated catalase levels.

"THP reversed the FST-induced OS. The study provides the first evidence for an antioxidant potential of THP".

Schizophrenia
- THP dose-dependently increased the haloperidol-induced catalepsy, decreased amphetamine-induced LA and apomorphine-induced climbing in mice. Pretreatment with RAMH reversed the effect of THP on catalepsy and apomorphine-induced climbing and only partially reversed the effect on amphetamine-induced LA.

"Our results indicate an antipsychotic-like profile of THP apparently mediated through the action on H₃ receptors".

Cerebral ischemia
- TBARS levels were elevated and reduced GSH and GST levels were reduced in the brains of MCA occluded rats. THP pretreatment significantly reversed the elevated TBARS levels but not the reduced GSH and GST. No change in catalase levels was observed in either MCAO or THP treated groups. A non-significant decrease in GPx, GR, and SOD levels was observed following MCAO. Pretreatment with THP further reduced the levels of these enzymes.

"MCAO produces oxidative stress. The dual effect (pro-and antioxidant) of THP discernible in our study raises doubt on its possible use in cerebral ischemia".

- MCA occluded rats showed significant decrease in nitrate and nitrite levels. Pretreatment with THP elevated the levels of nitrite.

"The opposite effects observed in NO levels require further investigations"
On the basis of above findings it may be concluded that:

H₃ receptor antagonists may represent a novel class of drugs and deserves more scientific attention for therapeutic potential in depression and schizophrenia. The added advantages being improved cognitive and vigilance effects and antioxidant effects. Effect of these ligands on cerebral ischemia requires further investigations. However, our findings are preliminary and a detailed investigation is required to explore the full potential of these ligands in depression, schizophrenia and cerebral ischemia and also in other conditions associated with oxidative stress.