SUMMARY AND CONCLUSIONS
Cognitive deficit is one of the major problems associated with epilepsy; both the underlying pathology and drug therapy can lead to disturbances in cognitive function. Unfortunately, at the present state of knowledge, a clear understanding of the mechanisms involved in the disease and, therefore, a rational therapeutic approach towards its effective management, is lacking. Are convulsions essential prerequisites of cognitive dysfunction? Is the latter unavoidable with AED therapy? Is histamine an important neurotransmitter for seizures? This study addressed several such questions in an effort to probe this problem with a focus on H3-receptor ligands, and search for suitable adjuncts to be used with AEDs for enhanced seizure control with minimal disease-associated and iatrogenic cognitive impairment.

Experimental models of convulsions (MES, PTZ, MSO) and tests for cognitive functions (PAP, SAP) and locomotor activity (videopath analyzer) in mice were used. The biochemical tools used included analysis of brain histamine and intracellular Ca2+ ion concentrations following various treatments. The authenticity of PAP as a true measure of cognitive function (irrespective of action on LA) was also looked into. The findings may be summarized as follows:

Epilepsy

1. Measurement of histamine in the whole brain and different brain regions (cerebral cortex, hypothalamus, brain stem, cerebellum and midbrain) following treatment with convulsants revealed enhancement with MES and reduction with PTZ. Varied effects on brain histamine levels were noted following treatment with different AEDs: increase (PHT and GBP), decrease (SVP) or no significant change (CBZ).

"Histaminergic mechanisms appear to play an important role both in seizures and in the action of AEDs".

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2. THP (a selective H$_3$-receptor antagonist) elicited anticonvulsant effects. The protection observed was marked and dose-dependent in the PTZ model but it was of substantially mild intensity against MES seizures. RAMH (a selective agonist for H$_3$-receptor) exhibited proconvulsive tendencies. It reversed the protection afforded by THP against both seizure models.

"The anticonvulsant effects of THP were apparently mediated through its action on H$_3$-receptors. This is the first experimental evidence for a protective action of any H$_3$-receptor antagonist against PTZ-induced clonic convulsions".

3. Interaction of selective H$_3$-receptor ligands (THP and RAMH) with some AEDs (PHT, CBZ, SVP, GBP) on experimental convulsions (MES, PTZ) yielded interesting results: protective effect following combined treatment with subeffective doses of THP with PHT (additive action) and GBP (synergistic action) and a reversal of such protection by RAMH.

"There are indicators (1 and 3) for the involvement of histaminergic mechanisms in the anticonvulsant effects of PHT and GBP. H$_3$-receptor antagonists hold promise to be effectively combined with low doses of AEDs for therapeutic advantage: additive/synergistic effects on anticonvulsant efficacy and reduced risk of dose-related toxicities."

4. SVP and GBP exhibited a protective action against MSO-induced convulsions. The latter were not modulated by THP and RAMH alone or by the combination of THP with SVP or GBP.

"There is no evidence for the mediation of MSO-induced convulsions via histaminergic mechanisms."
Cognitive functions

5. ES (both maximal and sub-convulsive) produced an impairment of cognitive function in PAP and SAP task. PTZ produced a dual effect: enhancement at lower (sub-convulsive) and impairment in both tests at higher (convulsive) doses.

"Convulsions may not be essential prerequisites for cognitive dysfunction."

6. Different AEDs affected cognition differently with some drugs impairing (PHT and SVP) and others enhancing (CBZ and GBP) performance in PAP and SAP tasks.

"The results hold promise in choosing a drug with minimal (or hopefully no) adverse effects on learning and memory."

7. THP improved cognitive performance in both PAP and SAP tasks. While RAMH elicited no significant effects on PAP, but improved performance on SAP. The latter could be related to an increase in LA.

"The study provides further evidence of the procognitive effects of H$_2$-receptor antagonists."

8. Pro-cognitive effects of THP and TAC on SAP were found to be synergistic.

"The association of tacrine with H$_2$-receptor antagonists may represent a novel therapeutic approach to cognitive dysfunction."
9. THP and BM (nootropic plant extract) protected against AEDs (PHT and/or SVP) - induced cognitive deficits without compromising on their anticonvulsant efficacy.

"THP and BM deserve more scientific attention for exploitation as adjuncts to AED-therapy."

10. Experiments devised to probe the value of PAP test as a true measure of cognitive function without being influenced by LA, revealed: a) a direct correlation between LA and SDE, b) no such correlation between LA, SDL and TSZ, and c) consistent effects on TSZ: increase with amnesic agents and decrease with nootropic drugs.

"LA influences PAP. Choice of parameters is crucial; TSZ appears to be the best indicator of cognitive function."

Intracellular \( \text{Ca}^{2+} \)

11. THP and GBP exhibited a marked concentration-dependent reduction of intracellular \( \text{Ca}^{2+} \) concentrations in the whole brain synaptosomes. RAMH showed no effect.

"Intracellular \( \text{Ca}^{2+} \) may be a direct target for the anticonvulsant and cognition facilitating effects of GBP and THP. A neuroprotective role is suggested."
On the basis of the above findings, it may be concluded that:

(i) Histaminergic mechanisms play a significant role in seizure generation and its control.

(ii) H<sub>3</sub>-receptor antagonists may represent a novel class of AEDs with therapeutic potential as adjuncts to conventional drugs, especially in patients where iatrogenic drug effects (cognitive and vigilance problems) greatly compromise the quality of life.

(iii) Designing AEDs with a mechanism-specific approach targeting histamine deserves more scientific attention.

(iv) Choosing an AED (eg CBZ and GBP) with minimal or no adverse effects on cognition might be a real option and needs to be explored completely.

(v) Neuroprotective potential of THP and GBP deserves scientific investigations for possible therapeutic applications in varied clinical conditions associated with intracellular Ca<sup>2+</sup> accumulation e.g. epilepsy, Alzheimer’s disease, Parkinson’s disease, Ischemic brain injury etc.

These leads deserve to be followed up with more intensive experimental, biochemical and clinical investigations to explore the full potential of rational polytherapy in epilepsy aimed at maximum seizure control with minimum side effects and discomfort to the patient.