The Cannabinoid-Memory and the Angiotensin-Memory Paradoxes: Another Penrose Triangle?

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***Abstract*— This study aims to evaluate the efficacy of two different drugs in their effects on memory and discrimination learning in a dual, controlled mouse model of amnesia, and to relate the findings to their pharmacokinetic and pharmacodynamics profiles. It also aims at validating a sub-acute scopolamine dose protocol as a model of rodent amnesia, specifically of emotional memory.**

The Exteroceptive models used include a Y-maze and an Elevated plus Maze (EPM). The Interoceptive models used are two different dose protocols of an amnesic drug, Scopolamine in forty-eight Swiss Albino mice, categorized into an acute and a sub-acute induction division, each of which later received fixed human equivalent doses of two drugs, apart from saline and scopolamine. Each animal was then evaluated for their Novelty Object Recognition (NOR) memory, and visuo-spatial memory, on the Y-maze and the EPM, respectively. The results of the Novelty Preference Test (NPT) and EPM test were analysed using Analysis of Variance.

The efficacy of Rimonabant in improving NOR memory was statistically higher than in saline and model control groups, more so in the acute induction. Its efficacy in enhancing visuo-spatial memory was less, although comparable to that on NOR memory. The efficacy of Valsartan was lower than the NOR Recognition Indices of other groups, although insignificant statistically. Sub-acute induction resulted in increased amnesia and anxiety in the Valsartan group on both mazes, the former being comparable to that noted in scopolamine group.

Rimonabant is a memory enhancer, in terms of both recognition and spatial memory. Valsartan is a pro-amnesic drug in a sub-acute induction, in which it lead to increased anxiety additionally. Hence, sub acute scopolamine protocol could be a novel model of emotional memory. Though many drawbacks were noted in the study, the drug effects could be explained by pharmacokinetic data and pharmacodynamic effects. This pilot study could be used for correlating the results in human conditions involving memory.

Index Terms*— *Cannabinoid Receptor, Angiotensin Receptor, Rimonabant, Valsartan, acute Scopolamine amnesia, maze learning, novelty object recognition memory, spatial memory, sub-acute scopolamine amnesia, y-maze, elevated plus maze

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I. Introduction

Angiotensin is a group of peptides consisting mainly of Angiotensin I, Angiotensin II, Angiotensin III, and Angiotensin IV. Each of these molecules can activate specific receptors for Angiotensin, named AT 1-4. Although each of these receptors has specific agonists and antagonists, they could, in theory, be occupied by any of the above peptide ligands.

Almost all the components of the Angiotensin system are found in the central nervous system. They regulate many physiological and pathophysiological processes and are responsible for maintaining vital functions, ranging from blood pressure regulation to sexual function. Perhaps the most important of these functions relevant to the current study is memory and its regulation and modulation.[1]

Similar to this system in its central role, is the endocannabinoid system. This system consists of two well characterized (CB1, CB2) and one poorly characterized receptor (Anandamide Receptor).[2] The endocannabinoids are a group of lipid-derived compounds including Anandamide (AEA), Virodamine, Noladin Ether, Δ 9-Tetrahydrocannabinol, and 2-Arachidonyl derivatives.

Cannabinoids mediate dopamine induced increase in reward behaviour through activation of CB1 receptors in nucleus accumbens.[3] Rimonabant could act through this pathway in the brain to increase acquisition of reward memory induced by psychostimulants like cocaine. Moreover, disrupting CB1 signalling by knocking out CB1 gene and then treating the mice with Rimonabant repeatedly impairs spatial memory extinction on Morris water maze.[4] There is also evidence that endocannabinoids affect inhibitory avoidance learning, but their effects on working long term memory lack proper evidence.[5]

On similar lines of reference, Angiotensin system through AT4 receptors and AT1-containing neurons in areas of brain, mediate memory and learning.[6] Angiotensin IV-mediated antagonism of hippocampal neurotransmission using an AT4-specific antagonist attenuates acetylcholine release.[7] It has already been an established fact[8] that increases in hippocampal acetylcholine improves memory and even prevents memory decline due to deposition of insoluble beta amyloid in brain.[9,10] Hence, we tried to evaluate whether or not Rimonabant and valsartan, acting through distinct mechanisms, improve working long term memory and spatial-emotional memory.

This study aims to evaluate the acute and sub-acute

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efficacies of Rimonabant and Valsartan in improving cognition in scopolamine mouse model of amnesia.

The hypothesis was that administering each drug to different groups of animals treated with memory disruptor anticholinergic, scopolamine, could lead to memory changes related, in some way, to the cholinergic system.

II. Materials & Methods

A. Ethical & Regulatory Considerations:

The study was accepted and permitted ethically by the Institutional Animal Ethics Committee (IAEC Approval Number: SRU/CEFT/LE/016/111/2009, dated 06 August 2009), and was conducted in a laboratory-cum-animal facility (SRU-CEFT) following Committee for the Purpose of Control & Supervision of Experiments on Animals (CPCSEA) and Good Laboratory Practices (GLP) guidelines.

B. Materials:

Scopolamine was purchased from Sigma-Aldrich, India, and the study drugs Valsartan and Rimonabant were purchased from local manufacturers. Mazes used for this study were of the standard dimensions:

EPM : 18 cm × 5 cm × 37 cm
Y-maze: 75 cm × 16 cm × 35 cm,
* Dimensions of each maze = length (total) × breadth (total) × height (total). The following figures (Figs. 1 & 2) depict the design of these mazes used in this study.

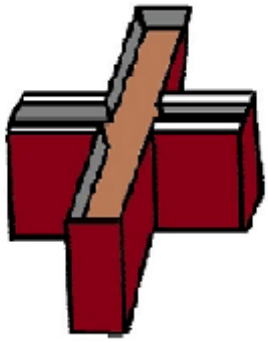


FIGURE 1: Mouse Elevated plus Maze; Note the enclosed arms have thicker walls (in white shade) and open arms have no walls (shown here as having a thin layer of single wall)

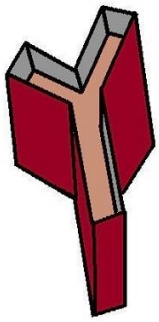


FIGURE 2: Y-maze: Note the two arms, novel and start arms are of equal lengths; the third longer arm is the familiar arm (not shown: the guillotine door in the central platform, adjacent novel arm opening).

The study drugs: Rimonabant is a Cannabinoid receptor partial antagonist that was initially approved for treatment of obesity as an anorectic drug and later retracted due to high incidence of suicidal tendencies. Valsartan is an Angiotensin receptor antagonist that is also used clinically as antihypertensive drug. Both were given separately to two different groups by oral gavage. Rimonabant was given as a 3% solution in water, whilst valsartan as a 10% aqueous solution.

Controls: Saline 0.5% was used to serve as non-vehicle non-treatment control for the first group. Scopolamine 3% in water served as the memory decline control for the acute study, whereas scopolamine 0.5% in water served as the amnesia control for the sub-chronic study. The study design and duration did not warrant the need for ageing control to remove ageing-related amnesia as a confounder.

Saline and scopolamine were both given by intra-peritoneal route. Scopolamine was injected also in the two test groups, prior to drug treatments.

Animals & grouping: Forty eight Swiss albino mice were obtained and grouped into two divisions – acute and sub-acute amnesia induction divisions. Under each division, four equally numbered groups were obtained randomly as per body weight using a table of random numbers.

Exteroceptive models: A study plan using a y-maze protocol was used to evaluate the working and novelty preference long term memory. On similar lines of reference, an elevated plus maze protocol was used to evaluate the spatial long term memory. Both forms of memory were not evaluated using the test drugs before. Both mazes were also used to study other possible effects like those on anxiety, behaviour, and motor activities.

Interoceptive models: Scopolamine was used to induce amnesia as a single high dose (acute amnesia) and as multiple daily once low doses for seven days (sub-acute amnesia). As it disrupts muscarinic system-mediated cholinergic transmission, it was the best Interoceptive model for the present study.

The following diagram depicts the animal grouping, treatment and evaluation plans (Fig. 3):

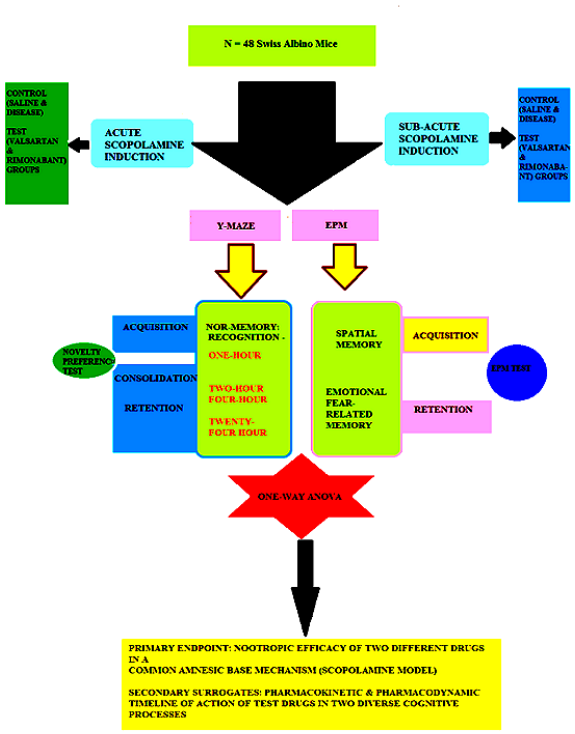


FIGURE 3: Study Grouping and Treatment-Evaluation Plan

C. Methodology:

Each division was assessed for the parameters using separate animals.

Y-Maze: The novelty preference test (NPT) was used to assess the working long term memory and novelty memory on y-maze after acute and sub-acute scopolamine treatment. In this test, the asymmetrical y-maze was used (refer figure 2), in which two arms were of equal dimensions, the third being longer in length. One of the equal arms had a guillotine door near its junction with the central platform, where all three arms meet.

This door was designed in a manner so as to allow opening or closing of this arm, as and when required. This arm equipped with the door was the novel (N) arm; the other equivalent adjacent arm was the start (S) arm; the longer arm was the familiar (F) arm. The familiar arm was longer so as to neutralize the confounding effects of initial exploratory trials in its longer length, relative to the novel arm which was closed in these trials.

The recognition index (R.I.) was used in later acquisition trials (one hour, two hour, four hour, and twenty four hours, post last drug treatment). It is a measure of novelty preference working long term memory, based in the hippocampal pathways. It is calculated using the formula:

$$R.I. = \frac{NAE\,(N)}{\{NAE\,(N) + NAE\,(F)\}} \geq 0.6\ (\geq 60\%\ as\ 'normal'\ exploratory\ values)$$

Where,
R.I. = Recognition Index,
NAE = Number of Arm Entries,
N & F = Novel & Familiar arms.

EPM: The transfer latency (T.L.) test was used to assess the spatial memory that was fear-related. The maze consisted of four arms of equal dimensions at ninety degrees orientation to each other in the horizontal plane, elevated from the floor. The two opposite pairs of arms differed from each other, in that one pair was open (no walls), the other one enclosed (surrounded by walls on all three sides, except that facing the central platform). In this test, in a single trial each in the two divisions, the mouse was placed in the central platform, that it faced one of the open arms. The upper cut-off time was 90

Seconds, above which if the mouse did not move into either of the enclosed arms, three fourths of its body length inside the arm, it was discarded from the study. The endpoint was transfer latency, the time taken by it to move from its starting initial position in the maze to this enclosed arm, is a direct measure of its Nootropic effect, inversely its anxiogenic effect.

Scopolamine Treatments: Scopolamine is an anticholinergic drug used as a transdermal therapeutic system in patients with motion sickness. It is also an amnestic agent, when injected in rodents.

In the acute amnesia induction, it is injected by intraperitoneal route as a single high dose of 3 mg/kg in mouse. This was followed by single oral drug treatments.

For the sub acute induction, it can be injected in multiple low doses on a daily basis for 7, 14, 21 days. In the present study, it was used as a daily 0.3-0.5 mg/kg injection for seven days, followed by drug treatments for an another three days.

D. Statistical Analyses:

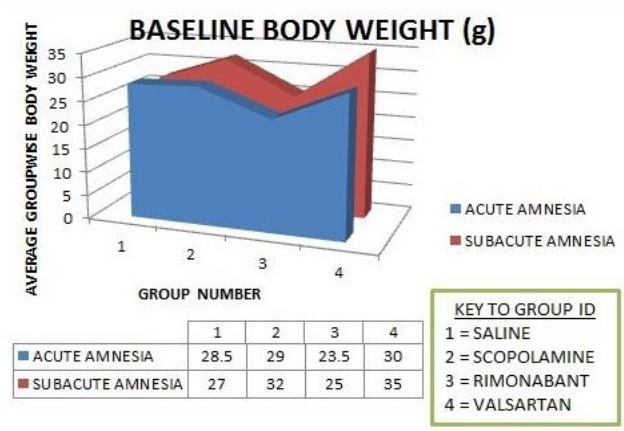
Single factor analysis of variance (ANOVA) was used to compare all the parameters in each group, followed by appropriate post-hoc tests like Tukey test or Bonferroni-Holm test. Statistical significance was kept at less than five percent.

All tests were performed using MS-excel 2010 and Daniel XL-toolbar, a statistical add-in for MS-excel.

III. RESULTS

A. Baseline characteristics:

The body weight of all the animals used fell in the 23-36 g range at the baseline. They were then randomized based on these weights into two divisions, presumably weighed equally group-wise. The numbers of male and female mice in each division were comparable.



	1	2	3	4
ACUTE AMNESIA	28.5	29	23.5	30
SUBACUTE AMNESIA	27	32	25	35

FIGURE 4: Baseline Body Weight Characteristics

B. Y-maze: latency to locomotion:

Post analysis of variance of the data depicted in figure 5, one can deduce that the comparison of sub-acute induction valsartan group was significantly different from the latencies in all other groups, although equal variances could not be assumed ($p < 0.05$). From figure 5, one can infer the above result since, it is that only group latency that is deviating from the normal value (since rodents are exploratory, latency will normally expected to be zero seconds).

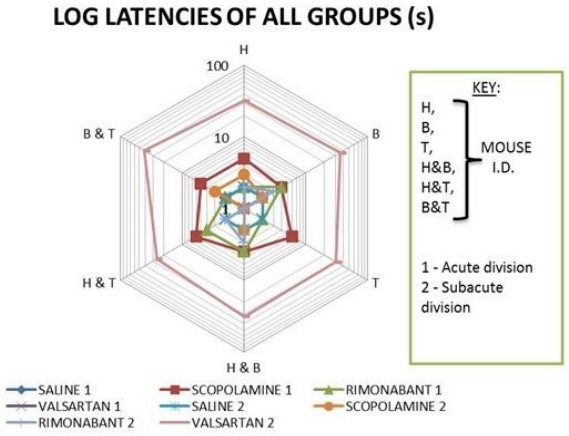
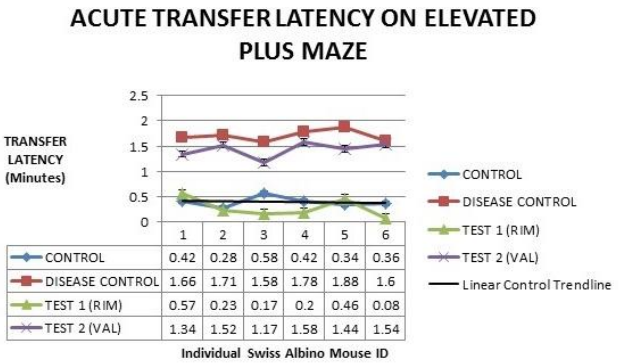


FIGURE 5: Shows semi-logarithmic plots of latencies to locomotion (seconds) of all groups in each division (centripetal axis) against individual mouse ID (circumferential axis)

C. Acute division: elevated plus maze:

The acute scopolamine induction in mice and the subsequent testing of spatial memory on the elevated plus maze showed statistically significant intergroup comparison differences in the transfer latencies between all two-group comparisons except that between Rimonabant group and saline control group ($p = 0.14$).

This would mean that the Rimonabant group did not differ significantly in its Nootropic efficacy as the saline control group. Additionally the Valsartan group was comparable to the scopolamine group in its pro-amnestic efficacy in a statistically significant manner ($p = 0.001$). The following figure (Fig. 6) summarizes these results:



	1	2	3	4	5	6
CONTROL	0.42	0.28	0.58	0.42	0.34	0.36
DISEASE CONTROL	1.66	1.71	1.58	1.78	1.88	1.6
TEST 1 (RIM)	0.57	0.23	0.17	0.2	0.46	0.08
TEST 2 (VAL)	1.34	1.52	1.17	1.58	1.44	1.54

FIGURE 6: Depicts line plot of transfer latencies (seconds) of all four groups in acute amnesia division.

D. Sub-acute division: elevated plus maze:

In this test, one can appreciate from figure 7, that valsartan group is comparable to scopolamine group in its spatial memory disruption, compared to the other two groups. Note that 100% impairment refers to the condition when transfer latency approaches cut-off time of one and a half minutes.

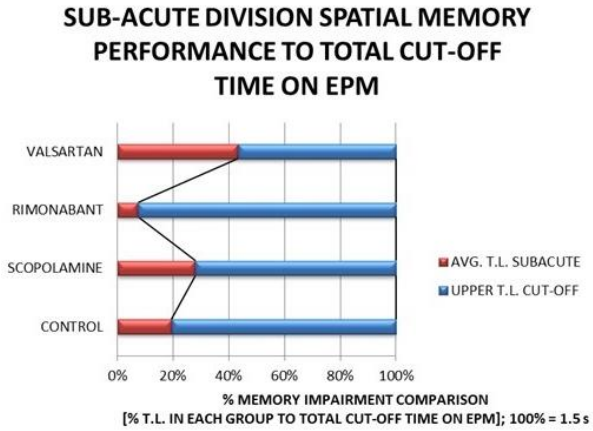
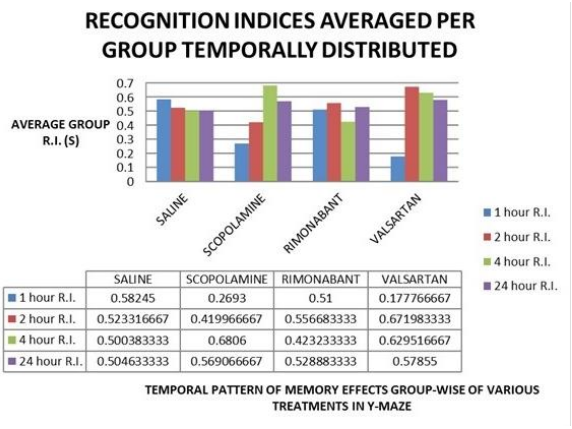


FIGURE 7: Group-Wise Spatial Memory Performance on EPM with the Trial Cut-Off as 100%; Sub-Acute Avg. T.L.

E. Y-maze: recognition indices:

Though the basic assumptions for ANOVA were met with reference to the y maze NPT, and further, an insignificant comparison ($p>0.05$), the results are important in explaining the temporal actions of the treatments on memory (Refer Figure 8 and discussion, later).



	SALINE	SCOPOLAMINE	RIMONABANT	VALSARTAN
1 hour R.I.	0.58245	0.2693	0.51	0.177766667
2 hour R.I.	0.523316667	0.419966667	0.556683333	0.671983333
4 hour R.I.	0.500383333	0.6806	0.423233333	0.629516667
24 hour R.I.	0.504633333	0.569066667	0.528883333	0.57855

FIGURE 8: Group-Wise Temporal Y-Maze Novelty Recognition Indexes Pattern

IV. DISCUSSION

A. Y-maze Results:

As notable form figure 9, the memory improvement was stable among the four groups in the acute amnesia model more than in the 24 hour trial. There tends to be better intergroup comparison in sub acute than in acute division, and a better improvement in working memory in 24 hour trial than in acute amnesia trials. Even in the sub acute division, performance was better in scopolamine and valsartan groups, as a paradox. Finally, Rimonabant group was borderline (0.6%) in its memory effects in sub acute division. The paradoxical effects could be partially explained by U-shaped dose response relationship that is inherent of most of the toxicological compounds like scopolamine.[11,12,13,14] Valsartan could follow similar effect relationship the peaks might be mediated by AT1 and later by AT4 receptors, the trough by AT2 receptors, owing probably to differential affinities of valsartan to these receptors.

Rimonabant did show borderline memory improvement which may be due to its multiple dosing which did not have the efficacy in modulating dopaminergic system transmission through CB1 receptors, and due to its unfavorable pharmacokinetics on repeated dosing.

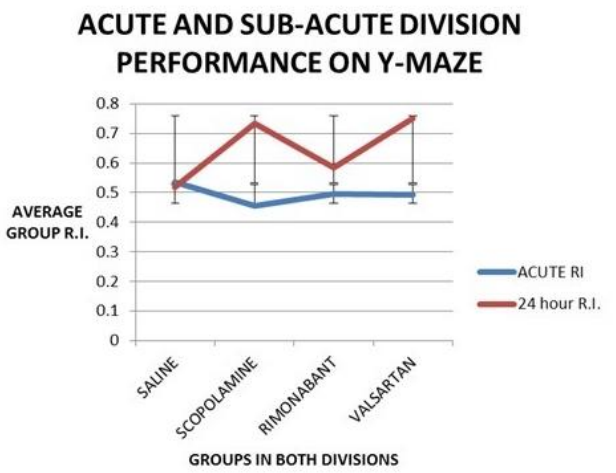


Figure 9: GroupWise Trend Lines for Y-Maze NPT Performances in Acute & Sub acute Amnesia (Error Bars Denote Avg. R.I. ± S.E.M.)

B. EPM Results:

From figures 6 & 7, one can conclude the similarly efficacious detrimental effects of both valsartan and scopolamine groups on spatial fear-related memory acutely and sub acutely. There was some improvement with Rimonabant treatment with spatial memory acutely. Of notable is that the valsartan showed increased anxiety on open arms on the EPM, as shown by transfer latencies approaching the cut-off times in the sub-acute amnesia model, and increased rearing on the open arms.

C. Extrapolation of the results to human beings:

The results could be extrapolated readily to human disorders like vascular and degenerative dementias. Rimonabant is moderately nootropic in acute dementia where spatial memory is disrupted, like delirium and Korsakoff Wernicke's psychosis and acute epileptic syndromes involving temporal lobes. Valsartan may be effective more in vascular than degenerative dementias like lewy-body and Alzheimer's' type; it may even cause working memory disruption in the latter types of dementias.

D. Pharmacodynamic & pharmacokinetic considerations:

Evidence also indicates the presence of interactive synaptic pathways and neural networks underlying the intertwined communicative neuroeffectors that could partly explain the drugs' effects observed in this study. [15] Indeed such interactions are now known to mediate key physiological processes, including those of cannabinoid, and, gastrointestinal with neurokininergic, [16] and cognitive and addictive behavior with glutaminergic and GABAergic pathways. [17] In contrast to Cannabinoid system, direct stimulation of cognitive processes by Angiotensin II [18] and Angiotensin IV [19, 20] ligands have been known, in-spite of controversial [21, 22, 23, 24 26] mechanisms. Interfacing such results with the accepted mechanisms of

memory processes evaluated in this study, and, using the results of this study, a working model could be developed for the memory actions of both study drugs, as follows (figure 10 & 11):

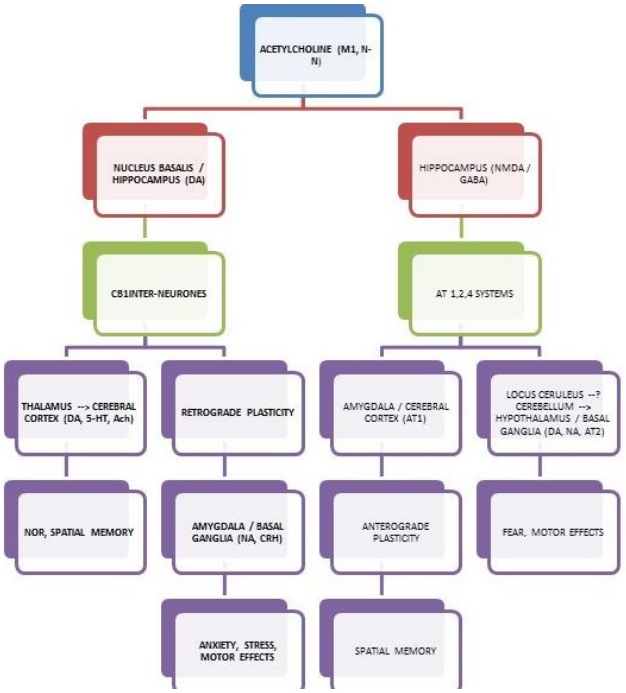


FIGURE 10: A WORKING MODEL TO EXPLAIN THE PHARMACODYMAMIC EFFECTS OF THE TWO DRUGS USED IN THIS STUDY (NOR = Novelty object recognition memory), M1, N-N, AT1-4 = Neurotransmitter receptors, DA, GABA, NMDA, 5-HT, Ach = Neurotransmitters, CRH = Hormonal transmitter

As the figure above (Fig. 10) clearly indicates, the three neuroeffector systems, viz. Muscarinic (represents Scopolamine model), Cannabinoid (represents Rimonabant's action), and Peptidergic (Angiotensin system represents Valsartan's mode of action) systems are intertwined in brain areas to display possibly the phenotypic results observed in this study.

The pharmacokinetic surrogate endpoints involved have not been summarized previously elsewhere as a timeline. Scopolamine follows "hormesis" dose-response curves (U-shaped in contrast to bell shaped) owing to its toxic mechanism on cholinergic system[14] in causing amnesia over its four-five half-live period. Note the dual-shaped nootropic-amnesic action of Valsartan, and bimodal action of Rimonabant as a nootropic agent, over each of their four-five half-lives, when the body concentration stabilize for such drugs.

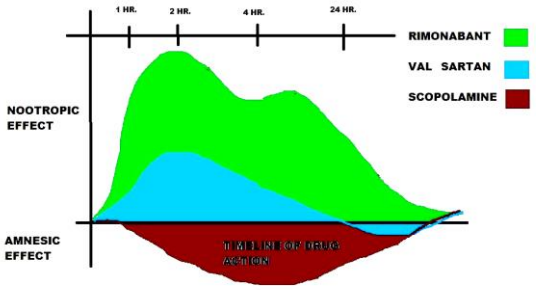


FIGURE 11: TIME-LINE OF ACTION OF THE STUDY DRUGS AND AMNESIC INDUCER ON BOTH FORMS OF MEMORY TAKEN TOGETHER (Figure not to scale)

The above figure (Fig. 11) states no more than that pharmacokinetic parameters must be carefully prioritized a-priori in planning such multi-drug-efficacy evaluations.

E. Drawbacks:

Although the study lacks statistical power and a considerable effect size, it must be considered as a pilot study, and encourage the evaluation of these drugs on memory both preclinically and clinically, since, Rimonabant could even reverse memory loss as a novel drug, whilst valsartan could be disrupting memory in hypertensive patients on this medication. Infact Rimonabant is known for its pleotropic effects in human beings.[25]

Biochemical parameters could not be evaluated herein due to financial constraints on the author.

F. Conclusion:

Both cannabinoid and angiotensin systems could play critical roles in cognition and behaviour, that could commonly be related to cholinergic system. The study must be definitely followed up by further evaluations, aiming to explain the paradoxes in this study.

Other forms of memory and cognitive processes must also be considered in the use of both the study drugs for further research and in clinical practice. Indeed this area of cognitive psychology remains unexplored, though it may be yet another impossible illusion much like the Penrose triangle.

FIGURE 12: The Impossible Penrose Triangle Illusion: The Cannabinoid-Angiotensin-Cholinergic interactions – how many such inexplicable areas are still hidden in cognitive psychology?

V. DISCLAIMER:

The author of the research entitled "THE CANNABINOID-MEMORY & THE ANGIOTENSIN-MEMORY PARADOXES: ANOTHER PENROSE TRIANGLE?" endorses the originality of the research, to his best professional competency. This original research of the aforesaid author was entirely carried out at CEFT, Sri Ramachandra Medical College & Research Institute, Chennai.

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