A NEW DOPAMINE AMINO-ACID CONJUGATE: PRECLINICAL *IN VITRO* STUDIES AND EVALUATION OF BEHAVIOURAL EFFECTS IN RATS.

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It is well established that alterations in the functionality of dopaminergic transmission are associated with neurodegenerative diseases such as Parkinson's Disease.

The purpose of this study was to investigate the activity of a new dopamine amino-acid conjugate: L-phenylalanine-β-(3,4-dihydroxyphenyl) etilamide (*DA-Phe*) in the central nervous system, by assessing its influence on different behavioural parameters in the rat.

Preliminarily, we tested the *in vitro* stability in plasmatic environment following the disappearance of *DA-Phen* from human plasma and the concurrent appearance of dopamine. Using rat brain homogenate, we also evaluated the level of *DA-Phen* cleavage by cerebral enzymes and the correspondent production of dopamine *in situ* [1]. Our *in vitro* data suggested that *DA-Phen* fulfills the pro-drug criteria and could be considered as a very helpful molecule able to cross the blood brain barrier and to explicate a CNS action.

On the basis of these results, we assessed some central pharmacological effects of *DA-Phen* on male Wistar rats, by the evaluation of some behavioural outcomes following i.p. administration of the prodrug.

Firstly, we assessed the effects of *DA-Phen* on behavioural reactivity in the Open Field (O.F.). The Elevated Plus Maze (EPM) test was also used in order to reveal anxiogenic- or anxiolytic-like properties of the administered compound. Both these tests highlight the conflict between the innate fear that rodents have for the central area (O.F) or open arms (EPM) of a novel maze versus their desire to explore new environments.

The forced swim test (FST) is the most widely used experimental model for assessing antidepressant activity of drugs, acting on noradrenergic and dopaminergic transmission. The test is based on the observation that, when placed into a cylinder filled with water from which they cannot escape, after a time of active swimming or climbing, rodents develop immobility, as a measure of despair behaviour. Therefore immobility time is considered as a measure of depressive-like behaviour. Antidepressant drugs can reduce the amount of immobility, or delay its onset, and/or increase active escape behaviours displayed during the FST [2].

For evaluating also the effects of *DA-Phen* on spatial learning and memory, the Morris water maze (MWM) was performed. In this test the rat is placed in a pool where he must use and remember visual cues located in the room in order to find a platform hidden underneath the surface of the water. The ability of the animal to retrieve and retain information acquired, or flexibility to purge and re-learn new strategies, can be determined using specific parameters (Escape Latency and Percentage of time spent in a specific quadrant) in a Reversal and a Probe trial [3].

Briefly, our results suggest that *DA-Phen* is able to affect behavioural reactivity and emotionality in the Open Field ($p<0.05$) and in the EPM ($p<0.05$). Also active behaviour in the FST appeared modified ($p<0.05$). At the same time, an enhancement in cognitive flexibility, and in the processing of spatial information was observed during the MWM, as a sign of a potentiation in the development of adaptative strategies in front of an aversive environment.

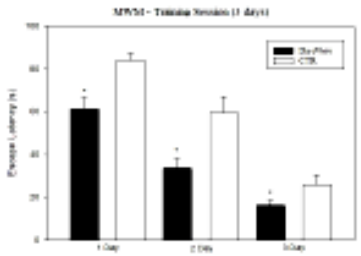

Fig.1 Training Session of MWM - Progressive reduction of Escape Latency time to reach the platform - : *DA-Phen* treated group, 0.03mmol/Kg; ? CTR group (saline, 0,9 % NaCl) $p<0.001$

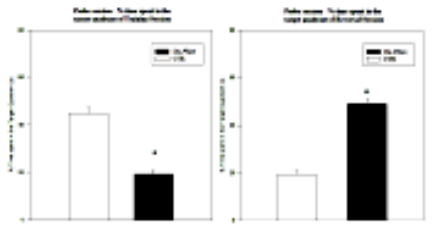

Fig.2 a, b. Probe Session of MWM – Percentage of time spent in the target quadrant of Training (a) and Reversal Sessions (b) – : *DA-Phen* treated group, 0.03mmol/Kg, ? CTR group (saline, 0,9 % NaCl) $p<0.001$

On the basis of our results *DA-Phen* appears to act like a dopamino-mimetic drug, and this pilot study shows how this drug could modulate mainly cognitive performances, which are strongly correlated with dopaminergic transmission.

References

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