XLI REUNION ANUAL
DE LA SOCIEDAD ARGENTINA
DE FARMACOLOGÍA EXPERIMENTAL

24 al 26 de Noviembre de 2009

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OI-05

LONG-TERM ANTICONVULSANT TREATMENT WITHOUT MEMORY IMPAIRMENT

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After more than a decade, the long-term clinical treatment with the anticonvulsant-antinociceptive drug gabapentin (GBP) is still related to adverse cognitive side effects. The administration of a single dose of GBP immediately after training improves retention performance of mice in an inhibitory avoidance task (IA). On the contrary, when GBP is given twice a day during 7 days, retention performance is impaired. In the present work we used a monolithic implant made of GBP-loaded poly(epsilon-caprolactone) matrices, which allowed the controlled release of the drug. When implants were inserted in a subcutaneous pocket in the side of the mice, immediately after training in the IA task, enhaced memory consolidation. Implants successfully protected against pentylenetetrazole-induced seizures by increasing not only latencies but also by decreasing the duration of convulsions. These results could lead to a clinically relevant conclusion: maintainance of stable GBP plasma levels protects against seizures without causing memory impairment. Hence, the adverse cognitive effects observed in the clinical practice could be avoided by stabilizing plasma levels of the drug.

OI-06

ARE GLUCOCORTICOIDS RECRUITING ENDOCANNABINOIDS TO MODULATE AVERSIVE MEMORY CONSOLIDATION IN THE HIPPOCAMPUS?

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The modulation of memory process is one of the several functions of the endocannabinoid system (ECS) in the brain, with CB1 receptors highly expressed in areas such as the dorsal hippocampus (HPC). Experimental evidence suggested an important role of the ECS in aversively-motivated memories. Similarly, Glucocorticoids (GC) released in response to stress exposure also modulates memory formation, and both stress and dexamethasone activate the ECS. Here we investigate the interaction between the ECS and GCs in the HPC in the modulation of fear memory consolidation. Two protocols with different shock intensities were used in order to control the level of aversiveness. Local infusion of AM251 into the HPC immediately after training was amnestic in the strong, but not the weak protocol. Moreover, AM251 was amnestic in animals stressed 0, but not 30 min prior to the weak protocol, reverting the stress-induced facilitating effect. Finally, intrahippocampal AM251 infusion reduced memory in animals that received dexamethasone immediately, but not 30 min before training. These results are consistent with the view that ECS is activated on demand, in a rapid and short-lived fashion. In conclusion, ECS interact with the GC in the dorsal hippocampus, a decisive memory-processing structure, suggesting a local GC-dependent ECS recruitment modulating the consolidation of an aversive memory.

OII-07

A MODEL OF METFORMIN ABSORPTION

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Metformin (Met) is a drug choice in Type-2 Diabetes and other related metabolic disorders treatments. Despite its wide use, Met absorption is poorly understood. Available data suggest that it is incomplete and saturable.

Aims: To analyze Met absorption in terms of a simplified kinetic model that could explain the low bioavailability and digestive intolerance of the drug.

Methods: We have recreated a three compartmental model of Met mass movement (intestinal lumen, enterocytes and blood) with three kinetics constants running in MS Excel® for Windows®.

Results: For a given dose of 500 mg, the model estimated masses (mg) were: absorbed (C3) = 192.63; stored in enterocytes (C2) = 121.04 and luminal (C1) = 186.3. The model constants (h^{-1}) were k13 ~ kabs = 1.1; k12 = 2.98 and k32 = 1.3. The acquired model data fitted well with the observed data for the first hour.

Conclusions: The obtained data have allowed a better estimated of Met absorption. Enterocyte drug accumulation precludes the respiratory chain activity, reducing the ATP levels and the glucose intestinal uptake. As a consequence, gastrointestinal side effects could be produced proportionally to Met accumulation.The discrepancy between simulated and observed data after the hour could be explained by the existence of a simultaneus distribution process in Met pharmacokinetics.

OII-08

COMPARATIVE PLASMA PHARMACOKINETICS, TISSUE DISTRIBUTION AND EFFICACY OF TWO FORMULATIONS CIPROFLOXACIN-BASED IN MOUSE-MODEL

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The aim of this study was to assess the plasma pharmacokinetics, tissue distribution and efficacy of a formulation ciprofloxacin (CIP)-Aluminum complex based (CIP-Al) in comparison with a conventional CIP formulation. For this study 96 Balb-C mice were divided in two groups and treated as follows: Group I received orally a single dose of CIP 5 mg/kg. Animals of Group II were identically treated but with CIP-AL formulation. Samples of blood, lung, intestine and kidney, were taken over 12 h post-treatment, and frozen until analysis by HPLC. The experimental efficacy study was based in an experimental *Salmonella* infection model in mice. Mice were divided into 3 groups: Control (distilled water treatment), CIP and CIP-Al. After 5 days of treatment survival was recorded. The plasma pharmacokinetics study outcomes revealed similar AUC values for CIP and CIP-Al. However, CIP concentration levels were statistically ($P< 0.05$) higher in lung, intestine and kidney after CIP-Al administration than those obtained for CIP conventional formulation group after 1h post treatment. The higher tissue concentrations of CIP-Al may have contributed to the observed efficacy trend where survived 33% of mice treated compared with the conventional CIP formulation assayed (0%). This fact would be related to the improved aqueous compatibility of CIP after aluminum complexation. We found that CIP-Al is at least as effective as CIP and exhibited advantageous pharmacokinetic and dispositional properties. It may become a valuable asset based on its formulation versatility due to higher solubility.