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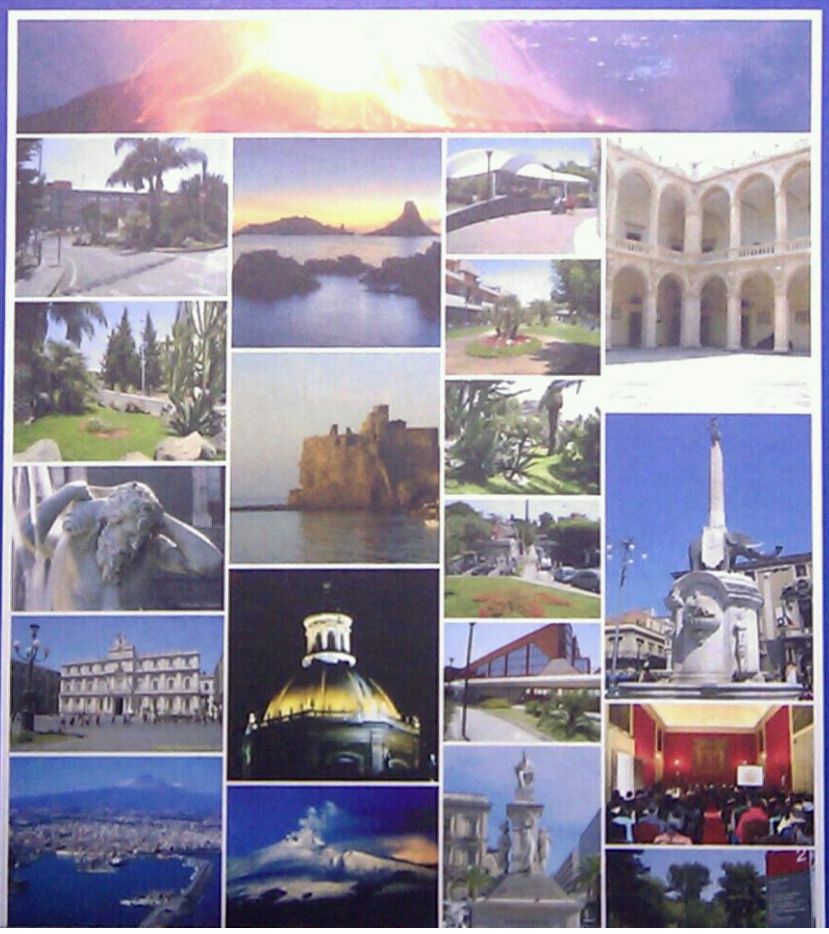

## EXPRESSION OF GAD ISOFORMS AND NEUROACTIVE AMINO ACID LEVELS IN MOUSE BRAIN AREAS: EFFECTS OF PENTYLENETETRAZOLE AND MINOCYCLINE

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Pro-inflammatory and anti-inflammatory molecules are synthesized in glial cells during epileptic activity in those brain areas, where seizures initiate and spread. Minocycline (MIN), a semi-synthetic, second-generation tetracycline analogue, in addition to its own antibacterial properties, exerts neuroprotective effects in various experimental models. The neuroprotective role of MIN has not been investigated in animal models of epilepsy. In this study, we investigated whether MIN is neuroprotective against pentylenetetrazole (PTZ)-induced seizure in mice and measured the levels of some neuroactive amino acids by HPLC and the expression of GAD65 and GAD67 isoforms by Western blotting. MIN was able to antagonize PTZ-induced seizure with an ED50 of 2.31 (1.25-4.27) mg/kg. Administration of PTZ led to an increase of GABA and glutamate in the cortex and a reduction in the hippocampus. Instead, the administration of MIN alone increased GABA and glutamate in both areas. Both GAD isoforms were increased by MIN and unmodified by PTZ in most brain areas studied. In conclusion, MIN shows good anticonvulsant properties in this animal model and the increase in GAD65 might underlie this effect.

## IN-VITRO EVALUATION OF NEW BENZOMORPHAN-BASED LIGANDS

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Unrelieved cancer pain significantly decreases the quality of life of patients. Cancer pain is a complex symptom associated with a range of diseases and is particularly difficult to treat effectively. In an first screening on benzomorphan-based compounds, LP1 was found to have affinity for μ and δ receptor in nanomolar range ($Ki_\mu$ = 0.83 nM and $Ki_\delta$ = 29,1 nM, respectively). Moreover, in tail flick test LP1 showed an analgesic effect comparable to morphine. In chronic subcutaneous administration, LP1 maintained its analgesic profile until the eighth day while chronic morphine administration determinated a significative loss of analgesic effect already at the third day of treatment. These results indicate that LP1 could be a new long-acting opioid compound with lower tolerance development. To evaluate its functional activity profile, LP1 was tested in the mouse vas deferens (MVD) isolated tissue assays and in [$^{35}$S]GTP$\gamma$S binding assay.