Presentation Abstract

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Title: The antinociceptive effects of L-kynurenine in the writhing test may be mediated by interaction kynurenic acid-GPR35

Location: Hall A-C

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Abstract: Kynurenine is the primary degradation product of tryptophan and the origin of the “kynurenine pathway”, a cascade of enzymatic steps that generate several biologically active compounds, including kynurenic acid (KYN) which has both neuroprotective and antinociceptive properties. KYN parenterally administrated crosses the blood brain barrier poorly but s.c. administration of 100 mg/kg kynurenine can increase kynurenic acid in the blood and in the brain (Chiarugi et al., J. Neurochem 67, 692, 1996) this effect being potentitated by probenecid, an inhibitor of organic anion transport. GPR35, a formerly “orphan receptor” activated by KYN, is highly abundant in DRG and possibly involved in nociception (Ohshiro et al., BBRC365, 344, 2008). The intraperitoneal injection of 0.6% acetic acid in mice induces the contraction of the abdominal muscles together with stretching of the hind legs (“writhes”). This so-called writhing test is used for antinociceptive screening and enables detection of compounds activity on acute pain. We examined the effects of L-kynurenine (KYN) alone and in combination with probenecid on the writhing and monitored the levels of plasma KYN from trunk blood after sacrifice at one hour following the drug treatments of mice. KYN (30, 100, 300 mg/kg s.c.) decreased the number of writhes by 16, 29 and 60% of controls, indicating an antinocicaptive/anti-inflammatory effect of the compound. KYN 100 mg/kg and 300 mg/kg dose-dependently increased plasma KYN to 1068±190 pmol/ml and 2201±213 pmol/ml (controls: 49±10 pmol/ml), respectively, suggesting that the antinociceptive effect of KYN was due to the increased availability of KYN. Co-administration of probenecid (200 mg/kg s.c) potentiated the antinociceptive effect of KYN (100 mg/kg) and increased plasma Kyna levels to 4610±712
pmol/ml. Probenecid by itself decreased the number of writhes and increased plasma KYNA to 268±87 pmol/ml. These results indicate that KYN has antinociceptive effects in the writhing test and suggest that KYNA mediated these effects.

**Disclosures:**  
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