**P34-1** The galanin-3 receptor (GALR3) antagonist, SNAP 37889, reduces operant responding for ethanol in alcohol-preferring (IP) rats

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The GALR3 subtype has been identified as having a role in alcohol consumption and feeding behaviour. The present study aimed to investigate the potential of the novel selective GALR3 antagonist, SNAP 37889, to reduce voluntary ethanol consumption in IP rats. To examine this aim, IP rats (n=12 per group) were trained to lever press for water and solutions containing either 10% (w/v) ethanol, 5% (w/v) sucrose or 0.1% (w/v) saccharin as part of an operant paradigm. Once a base level of responding was established, rats were pre-treated with SNAP 37889 (30mg/kg, i.p.) or vehicle 60 mins prior to operant sessions, after which the number of rewards obtained were recorded. In addition, rat locomotor activity was tested to determine whether SNAP 37889 had a sedative effect at the dose used in this study. Overall, treatment with SNAP 37889 (30 mg/kg, i.p.) significantly reduced operant responding for solutions containing ethanol, sucrose and saccharin: an effect independent of a sedative or anxiolytic property of the drug. These findings provide evidence that GALR3 antagonism reduces alcohol consumption and further suggests that GALR3 may be implicated in the rewarding effects of natural and drug reinforcers.

**P34-2** Time-dependent changes of EphA3 receptor expression in adult mouse hippocampus during LTP-like facilitation induced by nicotine

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We have previously reported that systemic application of nicotinic agonists induced a long-term potentiation (LTP)-like facilitation, a model of synaptic plasticity, in vivo in mouse hippocampus. The present study conducted to clarify localization and expression level of EphA3 receptor in synaptic plasticity by investigating the time-dependent change of the mRNA and protein levels during the LTP-like facilitation in mouse hippocampus. Immunohistochemical analysis showed that EphA3 receptor proteins were mainly expressed in mouse hippocampal neurons. The mRNA expression of EphA3 receptor was not changed 24 hr after application of nicotine (3 mg/kg). However, EphA3 receptor protein expression in mouse hippocampus markedly enhanced about 2.5-fold compared with control during 2 to 24 hr period by the same treatment, returning to the basal level in 72 hr. This enhancement of EphA3 receptor protein was inhibited by pretreatment of mecamylamine (0.5 mg/kg), a non-selective nicotinic acetylcholine receptors antagonist. These results suggest that EphA3 receptor protein enhanced by synaptic plasticity may contribute to long-lasting synaptic plasticity in mouse hippocampus.

**P34-3** Amelioration of cognitive deficits in AD-model mice with subchronic treatment of a γ-secretase modulator but not inhibitors

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Elevation of brain amyloid-β (Aβ) is thought to be a cause of Alzheimer's disease (AD). Gamma-secretase inhibitors (GSIs) reduce Aβ levels but increase β-carboxyl-terminal fragment of amyloid precursor protein (β-CTF), which may have deteriorating effects on synapses. We examined the effects of GSIs on cognition in AD-model and normal mice compared to a γ-secretase modulator (GSM), which lowers Aβ42 without increasing β-CTF.

Methods: A GSM (WQ0027125364) or GSIs (LY450139 or BMS-708163) were administered to APP transgenic (Tg2576) or wild-type mice. Y-maze tests were conducted to assess working memory, and brain levels of Aβ and β-CTF were measured via ELISA.

Results: Acute dosing with the GSM and GSIs significantly ameliorated the cognitive deficits in Tg2576. In contrast, subchronic dosing (6 days) with the GSIs failed to improve the deficits, although the GSM still improved them. Further, subchronic dosing with the GSM, but not the GSM, significantly impaired the working memory in wild-type mice. The maximum reductions of Aβ42 in Tg2576 were similar for all groups, but increases in β-CTF were found only in the GSM groups. Potential links between the increase in β-CTF and cognitive impairments remain to be elucidated.

**P34-4** GABA transporter 2 (GAT2/ BGT-1) may mediate the effect of betaine on water-immersion restraint stress-induced memory impairment

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Betaine (trimethylglycine) is a substrate of GABA transporter 2 in mice and is known as betaine/GABA transporter 1 in rats and human (GAT2/BGT-1). Although betaine improves memory impairment induced by lipopolysaccharide and water-immersion restraint stress (WIRS), the mechanism has not yet been elucidated. In this study, we used a step-down type passive avoidance test and real-time RT-PCR to investigate whether the effect of betaine on WIRS-induced memory impairment involves GAT2/BGT-1 or proinflammatory responses. Single administration of betaine 1 hr after WIRS prevented memory impairment on passive avoidance test. 7 days after WIRS, this memory improvement was blocked by co-administration of NNC 05-2090, a GAT2/BGT-1 inhibitor. Betaine might act on glycine sites of NMDA receptors, but its effect was not blocked by L-701,324, a glycine site antagonist. WIRS significantly increased mRNA expressions of interleukin-1β and GAT2 in the hippocampus 2 hrs after WIRS; however, betaine did not inhibit these mRNA expressions. These findings suggest that betaine improves WIRS-induced memory impairment via GAT2/BGT-1, but neuroinflammation may not be involved in this effect.