PM434
Haloperidol exerts depression-like behaviour in the forced swimming test while it has anxiolytic-like and analgesic effects in the elevated plus maze and hot plate tests: Altered gen expression levels of FGF2, synapsin and NGF in the hippocampus of mice.

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Abstract
Depression and anxiety is frequently seen in many schizophrenic patients and may be further aggravated or diminished by antipsychotic treatments. Haloperidol is a conventional antipsychotic used in schizophrenia and psychosis. Neutrophins are a family of structurally related proteins regulating the survival, differentiation, and maintenance of function of different neuron populations. Fibroblast growth factor-2 (FGF2) has an important role in many aspects of CNS functioning. Synapsin, another key marker of synaptic activity plays an important role in hippocampally based behaviors. There is evidence that nerve growth factor (NGF) also mediates multiple biological phenomena.

We aimed to investigate the effects of haloperidol on depression, anxiety and pain in naive mice, using forced swimming (FST), elevated plus maze (EPM) and hot plate tests. Since genes involved in neurite remodeling are among the primary targets of regulation, effects of haloperidol on expression levels of FGF2, synapsin and NGF in the hippocampus of mice were determined using quantitative RT-PCR.

Mice were treated chronically with haloperidol (0.125 and 0.25 mg/kg; 15 days, n=10/per group) and haloperidol was also administered intraperitoneally 60 min before the tests. Fluoxetine, diazepam or metamizol-sodium were used as reference drugs.

The results of this study revealed that: (1) In the FST, fluoxetine significantly decreased immobility time (p<0.001) while haloperidol significantly increased (0.25 mg/kg, p<0.05) this parameter. (2) In the EPM test, diazepam (p<0.001) and haloperidol (0.25 mg/kg) significantly increased % time spent in open arm's and % open arm entries (p<0.001; p<0.01). (3) In the hot plate test, metamizol sodium (p<0.001) and haloperidol (0.125 mg/kg and 0.25 mg/kg, p<0.05, p<0.001 respectively) significantly increased the latency for licking the hindpaws. (4) Haloperidol significantly increased expression of FGF2 and synapsin while it decreased expression of NGF. Thus haloperidol exerts depression-anxiolytic-like behaviour, analgesic effects and alters gen expression levels of FGF2, synapsin and NGF in mice.

PM435
Targeting Functional Selectivity of the Dopamine D2 Receptor for Treatment of Schizophrenia-like Behaviors
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Abstract
Ligand binding can lead to conformational changes in G protein-coupled receptors (GPCRs) that produce differential signaling events. These alterations can activate, inhibit, or exert no effects on the G protein-dependent signaling pathway while producing similar or diverse actions on the G protein-independent pathway through β-arrestin (βArr). This property of functional selectivity is novel and all approved drugs by the US Federal Drug Administration were not developed with this characteristic in mind. All current antipsychotic drugs bind to the dopamine D2 receptor (D2R). The purpose of our studies was to determine whether several βArr-biased compounds would show efficacy in two separate mouse genetic models of schizophrenia-like behaviors. The hypoglutamatergic NR1 knockdown (KD) and the hyperdopaminergic dopamine transporter knockout (DAT-KO) mice were subjected to behavioral tests for positive, negative, and cognitive schizophrenia-like responses. The D2R βArr-biased compounds, UNC9994 and UNC9975, were found to reduce hyperlocomotion in both NR1-KD and DAT-KO mice, whereas the compounds were only efficacious in normalizing prepulse inhibition in NR1-KD mice. The compounds also restored social behavior and novel object recognition memory in the two strains of mice. Using vesicular monoamine transporter 2 heterozygotes as a model for depressive-like behaviors, we observed that the UNC9995 decreased immobility in the tail suspension task to levels of the wild-type controls. Compared to haloperidol, catalepsy was very low with the UNC compounds. In summary, both βArr-biased compounds demonstrated efficacy in alleviating schizophrenia-like responses in the persistently hypoglutamatergic NR1-KD and the hyperdopaminergic DAT-KO mice. Together, these results suggest that βArr-bias may represent a unique approach for developing D2R drugs to treat schizophrenia and other related disorders in human patients. Supported by U19MH82441

PM436
A novel target for sensorimotor gating deficit: Cerebellar alpha6-containing GABA-A receptors
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Abstract
Previously, we found that a patient with intractable motor tic disorder, a spectrum of Tourette syndrome (TS), was responsive to the ground leaf juice of a local herb, Clerodendrum inerme (CI). Her tics subsided 1 hour after taking CI. No hemo-, renal- or hepatic toxicity was found after 2 years' follow-up.1 Using methamphetamine (MA)-induced hyperlocomotion2 and impairment of prepulse inhibition of acoustic startle response (PPI) in mice to model the hyper-dopaminergic characteristic of TS, we identified a CI active constituent, hispidulin. It is a flavonoid reported to be a positive allosteric modulator (PAM) of GABA, receptor α6, a sensorimotor gating receptor.3,4,5