BS05

Ketamine, relation to the NO-system and BPC157

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INTRODUCTION/OBJECTIVES: Ketamine is a NMDAR antagonist and can be used in rats for modelling "negative-like" behaviour symptoms resembling those in schizophrenia NMDARs function is linked with the NO-system. Modulating the NO-system with L-Arginine and L-NAME while antagonizing NMDAR could give insight on the potential treatment points of negative symptoms in schizophrenia. Stable gastric pentadecapeptide BPC 157 (Body protecting compound 157) has shown NO-system-modulating and dopamine modulating effects. We explored ketamine induced "negative-like" symptoms and the effects on BPC 157 on them.
MATERIALS AND METHODS: Male Wistar rats (200-250g, 12 weeks old) were used for the investigation. Ketamine was given intraperitoneally and dosed depending on the symptom investigated: 3mg/kg caused cognitive dysfunction, 30mg/kg caused anxiogenic effects and anhedonia, 8mg/kg for 3 days caused social withdrawal. Cognitive dysfunction was estimated with novel object recognition test, anxiogenic effects with open field test, anhedonia with sucrose test and social withdrawal with Koros test. L-NAME (5mg/kg), L-Arginine (100mg/kg) and BPC 157 (0.01mg/kg), were given alone or in combination, immediately after ketamine administration.
RESULTS: L-NAME and L-Arginine antagonized each other's activity when given together in the novel recognition test, which indicated that ketamine induced cognitive dysfunction is significantly NO- related. They didn't antagonize each other in ketamine induced social withdrawal, anhedonia, while they both had anxiogenic effects which indicate these effects are less NO-related. BPC 157 alone antagonizes cognitive dysfunction (by modulating the NO-system), social withdrawal, and anhedonia but promotes anxiolytic effects.
CONCLUSION: Further research will tell how BPC 157 modulates social withdrawal and anhedonia. Anxiolytic effects were described in previous investigations.

BS06

Synthesis and evaluation of biased agonists of immunometabolic receptor GPR84: a new class of immune cell modulators

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GPR84 (G protein-coupled receptor 84) is a Gαi-protein-coupled proinflammatory receptor that is mainly expressed on the innate immune system cells. DL-175 is a highly biased agonist of GPR84 which activates $G_{\alpha i}$ signaling pathways, with very low β-arrestin recruitment in cellular-based assays. This is coupled to low chemotaxis and high phagocytosis induction in macrophage functional assays (Lucy *et al*, 2019.). The purpose of this study is to investigate how the size of an attached hydrophobic moiety on DL-175 analogs correlates with activity and the potential improvement of metabolic stability compared to DL-175 when adding a fluorine atom which is a known xenobiotics metabolism blocker. We have designed, synthesized, and evaluated new potential GPR84 biased agonists: DL-175 analogs with variations on the linker and head part. Compounds VVR-014, VVR-016, VVR-018, and VVR-019 have been synthesized, characterized by Mass Spectrometry and Nuclear Magnetic Resonance, and evaluated in intracellular cAMP assays. VVR-016 and VVR-018 are inactive, VVR-014 has low activity (EC_{50} > 10 μM) and VVR-019 has modest activity (3.99 μM) in intracellular cAMP assays. VVR-014 activity in cellular cAMP assays suggests that its binding site has amino acids with larger hydrophobic residues leaving less space for a hydrophobic moiety on the compound. VVR-016 and VVR-018 inactivity suggests that pyridyl N-oxide hydrogen bond acceptor properties could be crucial for DL-175 activity. VVR-019 activity can be attributed to the smaller and less electron-dense tail group than DL-175 which suggests that a significant π-π interaction is happening in this part of the binding site.