BS05
Ketamine, relation to the NO-system and BPC157  
Ivan Maria Smoday, a Hrvoje Vranes, b Katarića Oroz, c Luka Ćorić, a Luka Kalogjera, a Mislav Pečnik, d Vilim Dretar e

a Department of Pharmacology; School of Medicine, University of Zagreb

DOI: https://doi.org/10.26800/LV-144-supl2-BS05

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  
Vanessa Rogga, a Pingi Wang, b Vincent Luscombe, c Angela Russell b,d

a Faculty of Pharmacy and Biochemistry, University of Zagreb  
b Department of Chemistry, University of Oxford, United Kingdom  
c Sir William Dunn School of Pathology, University of Oxford, United Kingdom  
d Department of Pharmacology, University of Oxford, United Kingdom

DOI: https://doi.org/10.26800/LV-144-supl2-BS06

INTRODUCTION/OBJECTIVES: 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 Gαi 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 (EC50 > 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.