Symposium 2

organized by Helmut Schmidhammer

Novel ligands interacting with opioid receptors

Chaired by Helmut Schmidhammer and Masaaki Yoshikawa

Universal opioid receptor ligands – buprenorphine and related orvinols

Gerta Cami-Kobeci[1], Willma E. Polgar[2], Taline V Khroyan[2], Lawrence Toll[2],
Stephen M. Husbands[1]

[1]Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK; [2]SRI International, Menlo Park, USA

Background and Aim: The pharmacological profile of buprenorphine has some unique features, some of which are explicable by the slow onset and even slower offset of its interaction with μ opioid (MOP) receptors. As a MOP receptor partial agonist, buprenorphine would also be expected to show a ceiling to its opiate effects, in fact the level of effect from very high doses are lower than from intermediate doses. This has been suggested to be due to activation of the nociceptin/orphanin FQ (NOP) receptor at high buprenorphine concentrations. It was of interest to discover if analogues can be developed with even higher levels of NOP receptor activity.

Results: Binding data on the compounds synthesised suggest that it is the C20 substituent that occupies the putative lipophilic site in the NOP receptor, as required for high affinity binding. By varying this group, ligands with affinities from 8 nM–133 nM NOP receptors were generated (buprenorphine Ki-NOP 77 nM). Of the compounds with good NOP receptor affinity, efficacy at this receptor ranged from very low (5% of nociceptin) to moderate (58% of nociceptin) with buprenorphine being intermediate in this range (21% of nociceptin). One compound, BU08028, was found to have equal affinity at opioid and NOP receptors (all between 1.6–8.5 nM) and very similar activity to buprenorphine in the [35S]GTPγS assay, except having higher efficacy (48% of nociceptin) at NOP receptors. However, *in vivo*, BU08028 proved to be a MOP receptor agonist with morphine-like efficacy.

Conclusions: The first universal opioid receptor ligands have been developed, confirming that substantial NOP receptor affinity is possible within the orvinol series.

Acknowledgments:
NIDA grants DA020469 (SMH) and DA023281 (LT).