Project Details	
Project Code	MRCNMH26Ba Bailey
Title	Synthetic heroin: understanding the dangers of nitazene drugs
Research Theme	NMH
Project Type	Wet lab
Summary	Drug-related deaths are now at the highest ever recorded in the UK, the majority involving opioid drugs. Currently, a new class of synthetic opioids known as 'nitazenes' are being sold on the street and have already been the cause of several deaths. Yet, the pharmacology of nitazenes is poorly understood. Using a combination of electrophysiology, in vitro and in silico assays, and rodent behaviour, the student on this project will investigate the neuropharmacology of nitazenes, how they cause harm, and design ways by which their harm can be reduced.
Description	Drug-related deaths are now at the highest ever recorded in the UK. In 2020 there were nearly 1,200 drug overdose deaths, the majority of which were opioid overdoses. Opioid drugs, such as heroin, act on mu opioid receptors (MOPrs). MOPrs are widely expressed in the brain and, when activated, can cause analgesia, euphoria, and respiratory depression. Historically, heroin has been the most widely used opioid drug on the street. However, there has been a recent rise in the availability of synthetic opioids, particularly the class of drug known as 'nitazenes'. These have already been the cause of fatal overdoses and their use is predicted to rapidly rise [1], potentially leading to future public health crises. However, the pharmacology of nitazenes is poorly understood: how they interact with MOPrs, and what the implications are for risk of overdose and treatment of overdoses. This project aims to investigate the neuropharmacology of nitazenes using an interdisciplinary approach. The supervisory group will consist of 3 academics: Chris Bailey (Bath), Eamonn Kelly (Bristol) and Robin Corey (Bristol) with complementary expertise in a range of in silico, in vitro, ex vivo and in vivo techniques to investigate the actions of nitazenes at a receptor, cellular and system level. Conventionally, agonists at receptors were thought to differ only in terms of their affinity (how well they bind to the receptor) and their efficacy (how well they activate the receptor). Recently, we have shown that the effects of different agonists at opioid receptors can also depend on how they bind to the receptor [2], and whether the cell is depolarized or not [3]. Further, MOPrs are present in neurons both presynaptically (on nerve terminals) and postsynaptically (on cell bodies and dendrites). We have preliminary evidence that different agonists can preferentially signal through presynaptic receptors, due to presynaptic receptors being more mobile than postsynaptic receptors [4]. And other studies have shown that the specific G-protein signalling induced by different agonists can affect pre- vs. post-synaptic signalling [5]. This pre/post-synaptic 'bias' can have profound effects on an agonist's effects in the whole animal [5, 6]. This project will focus on determining the pharmacodynamic characteristics of nitazenes by using brain slice electrophysiology to

	determine their actions and presynaptic and postsynaptic MOPrs, in neurons responsible for the rewarding and respiratory depressant effects of opioids [7]. Additional insight will be gathered using in silico molecular dynamics studies [2, 8] and in vitro cell-based signalling assays [9] with the PIs in Bristol. Further, the effects of nitazenes in the whole animal will be assessed using in vivo behavioural assays of reward/addiction and respiratory depression [10, 11] This project will give the student high-quality training in a broad range of techniques, all aiming to provide a comprehensive assessment of nitazenes at the receptor, cellular and whole-animal level. The ultimate goal will be to understand their relative harms of nitazenes and inform novel approaches to decrease those harms. **References** 1. Griffiths PN et al (2024) Addiction DOI: 10.1111/add.16420 2. Sutcliffe KJ et al. (2022) Adv Drug Alcohol Res; DOI: 10.3389/adar.2022.10280 3. Ruland JG et al (2020) Br J Pharmacol; DOI: 10.1111/bph.15070 4. Jullie D et al (2020) Neuron; DOI: 10.1016/j.neuron.2019.11.016 5. Wall MJ et al (2022) Nat Commun; DOI: 0.1038/s41467-022-31652-2 6. Montandon G et al (2016) Anesthesiology; DOI: 10.1097/ALN.0000000000000984 7. Lowe JD & Bailey CP (2015) Br J Pharmacol; DOI: 10.1111/bph.12605 8. Maloney F et al (2022) Nature; DOI: 10.1038/s41586-022-04534-2 9. Ramos-Gonzalez N et al (2023) Br J Pharmacol; DOI: 10.1111/bph.16084 10. Wright VL et al (2019) Addict Biol DOI : 10.1111/adb.12624 11. Hill R et al (2018) Br J Pharmacol DOI: 10.1111/bph.14224
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