EDITORIAL

Opioid Research in the time of the Opioid Crisis

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The study of opioids has long fascinated pharmacologists. Indeed, the first paper in the first issue of the *British Journal of Pharmacology* (MacDonald et al., 1946) reported on the antinociceptive actions of the opioid analgesic pethidine (meperidine) and its derivatives using the hot-plate test, before we had any knowledge of opioid receptors or endogenous opioid peptides.

Of course, we now know the endogenous opioid system comprises four closely related G protein-coupled receptors (GPCR), mu- or MOPr, delta or DOPr, kappa or KOPr and nociceptin or NOPr (Alexander et al., 2021), together with their endogenous peptidic ligands, the enkephalins and endorphins. Morphine and related exogenous opioid drugs exert their beneficial effects almost exclusively through activation of MOPr and are the gold standard for the relief of moderate to severe pain. However, this beneficial action comes at a very high price, since MOPr agonists are rewarding, widely misused, and can cause lethal respiratory depression. According to the World Health Organization (WHO) approximately 115,000 people world-wide died of an opioid overdose in 2017 (WHO, 2021). The number of opioid overdose deaths has risen steeply in several countries since the 1990's, partly due to the increased use of opioids in the management of chronic pain and the appearance of highly potent opioids, in particular fentanyl and its derivatives (fentanyls), on the illicit drug market (O'Donnel et al., 2017). Moreover, the COVID-19 pandemic has added to the problem. For example, in the USA opioid-induced deaths in 2020 increased by approximately 20,000 (to almost 70,000) compared to 2019 levels, and more than 70% of these involved a fentanyl (Centers for Disease Control and Prevention, 2021). In 2021 deaths involving an opioid rose again to almost 90,000 (Centers for Disease Control and Prevention, 2022). Additionally, the number of people with Opioid Use Disorder (OUD), a chronic relapsing disease,

continues to rise; many of these individuals started on prescription opioids (Strang et al., 2020). Thus, there is an immediate need for new emergency treatments for opioid overdose but also a vital requirement for a better understanding of the underlying neuronal changes during chronic opioid use that could improve the management of OUD. Finally, the development of new safe analgesic agents that are effective in relieving chronic pain with reduced addiction liability, would help to lessen the transition from pain patient to a patient with OUD. In this themed issue is a collection of papers highlighting some of the basic, pre-clinical and clinical research on-going during this time of the opioid crisis.

As mentioned above, fentanyl and its derivatives, including designer fentanyls, are associated with many overdose deaths. In their review, Kelly and colleagues (2022) describe the properties of fentanyl that may differentiate it from other MOPr agonists. They explain that *in vitro* and pre-clinical studies do not fully rationalize why the fentanyls are so dangerous, though multiple reasons have been proposed. These include rapid onset of action, high lipid solubility, differences between *in vitro* and *in vivo* potencies, biased signaling, incomplete cross-tolerance to heroin, and induction of muscle rigidity. Of relevance to this paper, it should be noted that the structure of fentanyl bound to MOPr has recently been published (Zhuang et al., 2022).

MOPr agonist-induced respiratory depression is characterized by slow, shallow, and irregular breathing, followed by respiratory arrest. Opioids also impair chemoreflexes and upper airway patency and the more potent opioids induce rigidity in the intercostal muscles and diaphragm giving a ‘wooden chest syndrome’ that reduces the ability to breathe. The currently available

rescue agent to reverse opioid overdose is the non-selective opioid receptor antagonist naloxone. The shortcomings of naloxone are discussed by Batemen et al., 2022. These including the possibility that naloxone may not readily displace high affinity agonists such as the fentanyls, the short half-life of naloxone that allows for re-narcotization and the fact that naloxone will not counter respiratory depression caused by drugs that might be taken along with opioids. Finally, naloxone will interfere with opioid-induced analgesia and/or opioid substitution therapy. Their paper also reviews current understanding of the neural circuitry underlying opioid-induced respiratory depression, and how this knowledge will help identify non-opioid targets as rescue agents. For example, medications that stimulate respiration such as positive modulators of the AMPA receptor (a.k.a. ampakines) and agonists at serotonin or orexin receptors.

As mentioned above, polypharmacy is often an issue in opioid overdose situations. For example, about 30% of opioid deaths in the USA involve a benzodiazepine. While it is thought that the central depressant actions of the benzodiazepine are the reason behind this, Larsen et al, 2022 test the hypothesis that altered metabolism of opioids, specifically oxycodone, by benzodiazepines is a contributing factor to opioid overdose deaths. Their study shows that chronic administration of diazepam, or its more potent analogue diclazepam, to mice modifies the metabolism of oxycodone. By competing with oxycodone for metabolism by CYP3A4, these benzodiazepines shunt oxycodone metabolism to CYP2D6 resulting in increased levels of the potent metabolite oxymorphone. Measuring oxymorphone levels in OUD patients may identify patients at greatest risk. In another study of metabolizing enzymes, Gabel et al., 2022 suggests

the observed sex differences in opioid analgesia might be due to differences in the conversion of morphine in tissues of the central nervous system to its major metabolite morphine-3-glucuronide (M-3-G), giving a greater ratio of M-3-G to morphine in females compared to males. This could be important since there are published data that M-3-G administration counteracts morphine-induced antinociception.

The approved therapies for OUD, namely methadone, the buprenorphine-naloxone combination, and naltrexone are reviewed by Cao and colleagues (2022). They point out that neuroadaptations also occur in dopaminergic, glutamatergic, and GABAergic circuits. Consequently, their review considers evidence for non-opioid treatments for OUD, including dopamine D3 antagonists and 4-aminobutylguanidine (agmatine). Of the approved current therapies, methadone is a full MOPr agonist and is administrated in clinics to avoid diversion. Naltrexone and buprenorphine-naloxone combinations require detoxification prior to starting treatment to prevent a severe withdrawal response. Detoxification is a very unpleasant experience that can be immediately relieved with an opioid, and thus is an important factor contributing to continued drug seeking. Alvarez-Perez and colleagues (2022) suggest that increasing the levels of endogenous opioid peptides by inhibiting their metabolism with “dual inhibitors of enkephalinase enzymes” or DENKIs is a viable and safe way to reduce the severity of the opioid abstinence syndrome. In support of this, studies in heroin addicts have demonstrated opioid peptides can reduce the severity of withdrawal. Phase 1 and Phase 2 clinical studies reveal that the most advanced DENKI (PL37) is well tolerated and safe in humans by oral route. In a similar vein, Lee et al., 2022 discuss the possibility of increasing the

concentration of endogenous cannabinoids by inhibiting the enzymes responsible for their breakdown or by stimulating their release by peripheral neuromodulation, for example with a TENs device. They suggest that such an approach could be used to manage inflammatory or neuropathic pain, provide an opioid sparing effect, and limit analgesic tolerance to MOPr agonist drugs.

There is evidence for sex differences in treatment outcomes and complications of translation from animal models to human patients (Cao et al., 2022). The standard method to examine drugs for abuse liability and to evaluate treatments for substance use disorders including OUD is intravenous self-administration in rats or non-human primates, usually allowing the animals continuous access to the drug under study for a set time. D'Ottavio et al., 2022 report on an intermittent access model of heroin self-administration that better resembles the pattern of heroin taking in humans. Their method results in higher brain levels of heroin and 6-monoacetylmorphine than continuous access. It generates a stronger motivation for heroin and reveals a sex difference in cue-induced craving. The method should have more translational significance as we search for an understanding of OUD and medications to address the condition.

Agonist occupation of a GPCR activates, or inhibits, intracellular signalling pathways. This action is terminated by phosphorylation of the C-tail of the receptor by kinase enzymes and leads to the recruitment of β-arrestin followed by receptor internalization. The recruited β-arrestin can also interact with downstream effectors. Reports published about 20 years ago

indicated that the action of morphine was enhanced in mice lacking β-arrestin2 due to a reduced antinociceptive tolerance. Moreover, these mice were reportedly less sensitive to morphine-induced respiratory depression and constipation. This led to the hypothesis that G protein signalling was responsible for opioid-induced antinociception, whilst signalling downstream of β-arrestin was responsible for the adverse effects of MOPr activation. Unfortunately, this hypothesis has not stood the test of time. On the other hand, opioid ligands that preferentially activate G proteins should be less sensitive to tolerance development due to their lower ability to recruit β-arrestin. Several groups have sought to develop MOPr ligands that favour G protein activation over β-arrestin recruitment, so called "G protein-biased agonists". Arguably the most successful compound to come out of these drug discovery efforts is TVR130 (Oliceridine®), which has been approved in the USA as an injectable analgesic in hospital settings. Another popular example is PZM21; both compounds are reported to show reduced tolerance in preclinical studies. In a recently published paper Singleton and colleagues (2021) confirm that TVR130 does show reduced antinociceptive tolerance, but this can be explained by the partial agonist nature of the compound and depends on the number of MOPr's available. Related to this, Groom et al., 2022 describe studies of a peptidic G protein-biased agonist with similar efficacy as morphine. In neurons from the locus coeruleus this compound readily induces G protein receptor kinase (GRK)-mediated desensitization of MOPr, showing that a weak ability to recruit β-arrestin does not guarantee an absence of desensitization and tolerance. Moreover, this finding suggests the presence of a novel GRK-dependent, arrestin-independent mechanism of agonist-induced desensitization and subsequent tolerance development at MOPr.

Many people with OUD start off being treated chronically with opioid medications for pain. In efforts to improve the clinical profile of morphine a “photopharmacology” approach has been designed by López-Cano et al., 2022. This group synthesized a photocaged morphine that is activated by light. In a proof-of-concept study using rats, they demonstrate that photoactivation of caged morphine externally in the hind paw or by spinally-implanted fiber optics, will inhibit the noxious responses caused by formalin injection into the hind paw. Thus, opioids can be locally activated with high spatiotemporal resolution, potentially minimizing adverse effects. Varga et al., 2022 identify ways to target MOPr that might be safer than traditional opioid drugs, including biased agonism and allosteric modulation. Their review also discusses compounds that interact with two GPCRs simultaneously, or target heteromeric GPCR complexes often, but not always, involving MOPr. This can provide for opioid sparing and/or may reduce the side-effects of the MOPr agonist. Much of the efforts in this direction have been preclinical to date, but Cebranopadol, which acts as an agonist at both MOPr and NOPr is currently in Phase 3 clinical trials for pain related to cancer**.** Gaborit and Massotte (2022) expand on the theme to provide evidence of a role for native heteromers containing an opioid receptor in reducing nociceptive signals in chronic pain states, with possible roles in psychiatric conditions co-morbid with pain. In addition, complexes comprising MOPr with ion channels have been identified. Studying the physiology of heteromers containing GPCRs in native tissues is challenging and likely will have to wait for the discovery of ligands specific for these macromolecular complexes.

We hope the papers in this theme issue of the *Journal* will inspire new ideas not only among the opioid research community, but also encourage pharmacologists working in other areas to bring

their experiences and techniques to bear to ensure better methods for the management of OUD, as well as improved ways to manage pain especially chronic pain, without the problems associated with traditional MOPr agonists.

References

Alexander, S. P., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Pawson, A. J., Southan, C., Davies, J. A., Abbracchio, M. P., Alexander, W., Al-hosaini, K., Bäck, M., Barnes, N. M., Bathgate, R., … Ye, R. D. (2021). The concise guide to pharmacology 2021/22: G protein-coupled receptors. Br. J. Pharmacol, **178** (S1), S27– S156.

Alvarez-Perez,.B, Poras, Hervé, P., Maldonado, R. (2022). The inhibition of enkephalin catabolism by dual enkephalinase inhibitor: a novel possible therapeutic approach for opioid use disorders. Br. J. Pharmacol. 10.1111/bph.15656.

Bateman, J.T., Saunders, S.E. Levitt, E.S. (2022). Understanding and Countering Opioid-induced Respiratory Depression. Br. J. Pharmacol. 10.1111/bph.15580.

Cao, D-N., Li, F., Wu, N., Li, J. (2022). Insights into the mechanisms underlying opioid use disorder and potential treatment strategies. Br. J. Pharmacol. 10.1111/bph.15592.

Centers for Disease Control and Prevention. (2021). Drug Overdose Deaths in the U.S. Top 100,000 Annually.
https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

Centers for Disease Control and Prevention. (2022). U.S. Overdose Deaths In 2021 Increased Half as Much as in 2020 – But Are Still Up 15%.
https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm

D'Ottavio, G., Reverte, I., Ragozzino, D., Meringolo, M., Milella,M.S. Boix, F., Venniro, M., Badiani, A., Daniele Caprioli, D. (2022). Increased heroin intake and relapse vulnerability in intermittent relative to continuous self-administration: sex differences in rats. Br. J. Pharmacol. 10.1111/bph.15791.

Gabel, F., Hovhannisyan, V., Andry, V., Goumon, Y. (2022). Central metabolism as a potential origin of sex differences in morphine antinociception but not in the induction of antinociceptive tolerance in mice. Br. J. Pharmacol. 10.1111/bph.15792.

Gaborit, M., Massotte, D. (2022). Therapeutic potential of opioid receptor heteromers in chronic pain and associated comorbidities. Br. J. Pharmacol. 10.1111/bph.15772.

Groom, S., Blum, N.K., Conibear, A.E., Disney, A., Hill, R., Husbands, S.M., Li, Y., Toll, L., Kliewer, A., Schulz, Henderson, G., Kelly, E., Bailey, C.P. (2002). A novel G protein-biased agonist at the μ opioid receptor induces substantial receptor desensitization through G protein-coupled receptor kinase. Br. J. Pharmacol. 10.1111/bph.15334.

Kelly, E., Sutcliffe, K., Cavallo, D., Ramos-Gonzalez, N., Alhosan, N., Henderson, G. (2022). The anomalous pharmacology of fentanyl. Br. J. Pharmacol. 10.1111/bph.15573.

Lawson, R., Čechová, P., Zarrouk, E., Javellaud, J., Bazgier, V., Otyepka, M., Trouillas, P., Picard, N., Marquet, P., Saint-Marcoux, F., El Balkhi, S. (2022). Metabolic interactions of benzodiazepines with oxycodone ex vivo and toxicity depending on usage patterns in an animal model. Br. J. Pharmacol. 10.1111/bph.15765.

Lee, MT., Mackie, K., Chiou, L-C. (2022). Alternative Pain Management via Endocannabinoids in the Time of the Opioid Epidemic: Peripheral Neuromodulation and Pharmacological Interventions. Br. J. Pharmacol. 10.1111/bph.15771.

López-Cano, M., Font, J., Aso, E., Sahlholm, K., Cabré, G., Giraldo, J., De Koninck, Y., Hernando, J., Llebaria, A., Fernández-Dueñas, V., Ciruela, F. (2022). Remote local photoactivation of morphine produces analgesia without opioid-related adverse effects. Br. J. Pharmacol. 10.1111/bph.15645.

MacDonald, A.D., Woolfe, G., Bergel, F., Morrison, A.L., Rinderknecht, H. (1946). Analgesic action of pethidine derivatives and related compounds. Br. J. Pharmacol, **1**, 4-14.

O'Donnel, J. K., J. Halpin, C. L. Mattson, B. A. Goldberg and R. M. Gladden (2017). Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 - 10 States, July - December 2016. Morbidity and Mortality Weekly Report **66**, 1197-1202.

Singleton, S., Baptista-Hon, D.T., Edelsten, E., McCaughey, K.S., Camplisson, E., Hales, T.G. (2021). TRV130 partial agonism and capacity to induce anti-nociceptive tolerance revealed through reducing available μ-opioid receptor number. Br. J. Pharmacol. 178: 1855–1868. https://doi.org/10.1111/bph.15409.

Strang, J., Volkow, N.D., Degenhardt, L., Hickman, M., Johnson. K., Koob, G.F., Marshall, B.D.L., Tyndall, M., Walsh, S.L. (2020) Opioid use disorder. Nat Rev Dis Primers. **6**, 3.

Varga, B., Streicher, J.M.,Majumdar, S. (2022). Strategies towards safer opioid analgesics - a review of old and upcoming targets. Br. J. Pharmacol. 10.1111/bph.15760.

WHO (2021). Opioid Overdose. https://www.who.int/news-room/fact-sheets/detail/opioid-overdose

Zhuang, Y., Wang,Y., He, B., He, X., Zhou, X.E., Guo, S., Rao, Q., Yang,J., Liu,J., Zhou,Q., Wang,X., Liu,M., Liu,W., Jiang,X., Yang, D.,

Jiang, H., Shen, J., Melcher, K., Chen, H., Jiang,Y., Cheng, X., Wang, M-W., Xie, X., Xu., H.E. (2022). Molecular recognition by morphine and fentanyl of the human mu-opioid receptor. Cell **185**, 4361- 4375