Pharmacogenetic Modulation of the Behavioral Effects of Buprenorphine in a Mouse Model of the OPRM1 (A118G) Polymorphism

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Background: Pharmacogenetic studies have identified the non-synonymous single nucleotide polymorphism (A118G) in the human mu opioid receptor (MOR) gene (*OPRM1*) as a critical genetic variant capable of altering the efficacy of opioid therapeutics including morphine and fentanyl. To date few studies have explored the potential impact of the OPRM1 gene on the therapeutic efficacy of buprenorphine (BPN), a potent MOR partial agonist and kappa opioid receptor (KOR) antagonist. BPN is approved by the FDA for the treatment of opioid addiction and chronic pain, yet there is a considerable lack of information pertaining to the OPRM1 A118G SNP in relation to BPN's effects. Therefore, the goal of this study was to determine whether the common single nucleotide polymorphism in the *OPRM1* gene, A118G, alters the efficacy of BPN in behavioral paradigms mediated by MORs.

Methods: All studies were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. Mice were generated on a C57BL/6 genetic background, and bred using a heterozygous breeding paradigm. Briefly site-directed mutagenesis introduced the polymorphism into exon 1 of the *Oprm1* gene, where the adenine (A) nucleotide at position 112 was changed to a guanine (G). This substitution is equivalent to that in the human *OPRM1* gene at position 118. Female mice with AA, AG and GG genotypes were used for all studies. BPN produced significant antinociception in the hot plate test, reduced the latency to start consuming a palatable food in the novelty induced hypophagia (NIH) test and induced robust psychomotor stimulant hyperactivity immediately following administration. These behavioral effects of BPN

are mediated by MORs. Therefore, the impact of the *Oprm1* A112G of BPN's effects was evaluated in these tasks and also in the forced swimming test (FST), where BPN produces significant reductions in immobility mediated by KORs.

Results: The maximal analgesic effect of BPN in the hot plate test was obtained in AA mice and significantly blunted in AG and GG mice (Genotype*Treatment Interaction; $F_{8, 156}$=2.608, p=0.010, AG v's AA p<0.01 at 3 mg/kg and GG v's AA p<0.05 at 1 and 3 mg/kg). Similarly, the BPN-induced reduction of latency to consume food in the NIH test in AA mice was blocked entirely in both heterozygous AG and homozygous GG littermates (Genotype*Treatment Interaction; $F_{2, 40}$=3.394, p=0.0435, AA BPN v's AA Vehicle p<0.05). In addition, GG mice exhibited marked reductions in psychomotor stimulant locomotor activity compared to the AA group, diminishing both horizontal ($F_{2, 72}$ =3.29, p=0.043, GG v's AA p<0.01) and vertical activity ($F_{2, 72}$=4.165, p=0.019 GG v's AA p<0.05). In contrast, reduced immobility in FST, an effect of BPN mediated by kappa opioid receptors, was not affected by genotype (main effect of treatment; $F_{2, 56}$=5.913, p=0.018).

Conclusions: These studies demonstrate the ability of the *Oprm1* A112G SNP to attenuate the analgesic, anxiolytic and hyperlocomotor effects of BPN. Overall, these data suggest that the *OPRM1* A118G SNP will significantly impact the therapeutic efficacy of BPN, especially if employed for chronic pain and opioid dependence. As such, clinical studies are required to fully explore the impact of *OPRM1* A118G SNP in different patient populations. These studies will be timely, given the recent effort to repurpose BPN for use as a therapeutic for major depressive disorder. Considering the increasing number of individuals prescribed BPN for its many indications and the large number of individuals diagnosed with depression and comorbid pain/addiction, such pharmacogenetic studies will provide invaluable assistance in improving clinical outcomes.