BALB/c substrain differences in whole brain concentrations of the highly potent oxycodone metabolite, oxymorphone map to chromosomes 5, 10, and 16 in a reduced complexity cross.

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Understanding the pharmacokinetic profile of an opioid drug is vital to therapeutic success, and mutations in human PK genes can alter the therapeutic efficacy of opioids. Oxycodone (OXY) is a semisynthetic opioid metabolized into noroxycodone (inactive, NOR) and oxymorphone (active, OMOR) by CYP450 enzymes, however there is limited knowledge regarding the transport of OXY and its metabolites in the brain. Our lab has observed that 30 minutes post oxycodone administration (1.25 mg/kg, i.p.), BALB/cJ mice show higher whole brain concentrations of oxycodone (t(14)=-2.55, p=0.023), noroxycodone (t(14)=-1.917, p=0.076), and oxymorphone (t(14)=-2.06, p=0.058) compared to the closely related BALB/cByJ substrain. This observation mirrors previous findings indicating BALB/cJ mice show increased state-dependent CPP compared to BALB/cByJ. We aimed to discover genetic factors underlying this difference by quantitative trait locus (QTL) mapping whole brain OXY, NOR, and OMOR concentrations in a reduced complexity cross (RCC). Because BALB/cJ and BALB/cByJ substrains differ by only ~11,000 SNPs, insertions, and deletions, large genetic loci mapped in F2 studies are offset by dramatically reduced density of potentially causal variants. QTL mapping in 119 BALB/cJ x BALB/cByJ F2 mice (59F, 60M) identified 3 loci on chromosomes 5, 10, and 16 significantly associated with OMOR concentration. Oxymorphone is a bioactive metabolite at the mu opioid receptor, with 8x the potency of oxycodone. Candidate PK-related genes within these regions include 18 SLC genes, but no CYP450, ABCs, or UGT genes. Future studies will overlay these findings with OXY behavioral QTLs and cis-eQTLs to identify candidate genes for validation.