

Mapping Opioid Receptor Occupancy of Varying Concentrations of Sustained-Release Naltrexone in Serum by PET Imaging

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Aims: Naltrexone is a competitive and non-selective opioid receptor antagonist used for the treatment of alcohol and opioid addictions. It effectively blocks opioid receptor (OR) binding sites against opioid agonists such as heroin. Positron Emission Tomography (PET) is an ideal tool for quantitative mapping of OR occupancy from decreasing concentrations of naltrexone in plasma from sustained-release naltrexone implants. In order to fully evaluate OR occupancy by Naltrexone, three structurally similar ¹⁸F-labeled OR PET tracers were chosen which have different OR binding properties; antagonist [¹⁸F]FDPN, partial agonist [¹⁸F]FBPN, and agonist [¹⁸F]PEO. (see abstract Schoultz et al.)

Methods: Ten rats were subcutaneously implanted with a tablet of sustained-release naltrexone. Six of the animals underwent baseline PET scans using all three tracers prior to implantation, and were scanned again in weeks 1, 6, 16, 26, and 29 post-implantation. Due to constraints in half-life and delivered tracer, only four animals underwent the full scanning regimen with [¹⁸F]FBPN. All animals were dynamically scanned for 60 mins, and specific binding (BP_{nd}) was calculated using a reference tissue model. Plasma concentrations of naltrexone were regularly sampled over the course of the 29 weeks.

Results: The blood sample analyses showed large inter-subject variability of Naltrexone plasma concentration. During the first weeks, Naltrexone blocked effectively all OR binding sites, but OR occupancy decreased with decreasing Naltrexone plasma concentration for all three tracers. At week 6 (Naltrexone mean concentration: 36.0 ng/mL), receptor occupancy of Naltrexone versus the three tracers was 91% for [¹⁸F]FDPN and 90% for [¹⁸F]FBPN and [¹⁸F]PEO. At week 26 (Naltrexone mean concentration: 3.4 ng/mL), receptor occupancy of Naltrexone versus the three tracers was 65% for [¹⁸F]FDPN, 48% for [¹⁸F]FBPN, and 47% for [¹⁸F]PEO. Significant correlation between Naltrexone concentration and BP_{nd} for all three tracers was observed: [¹⁸F]FDPN ($r^2=0.93$, $t(7)=9.3$, $p<10^{-4}$), [¹⁸F]FBPN ($r^2=0.89$, $t(6)=7.0$, $p<10^{-3}$), and [¹⁸F]PEO ($r^2=0.66$, $t(9)=4.2$, $p<10^{-2}$).

Conclusions: The uptake of all three OR tracers, agonist, partial agonist and antagonist, were effectively blocked by Naltrexone. At lower Naltrexone levels in plasma, there was still a significant displacement of the tracers, demonstrating that OR tracers in PET may aid in the assessment of treatment protocols with Naltrexone.