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DEVELOPMENT AND CHARACTERIZATION OF A METHODOLOGY FOR THE
SIMULTANEOUS AND INDIVIDUAL DETERMINATION OF IN VIVO RECEPTOR
OCCUPANCY AT MU, DELTA, AND KAPPA OPIOID RECEPTORS, AND
EXAMINATION OF THE EFFECTS OF OPIOID ANTAGONIST OCCUPANCY ON
FEEDING BEHAVIOR IN THE RAT

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Jay R. Simon Ph.D. – Chair



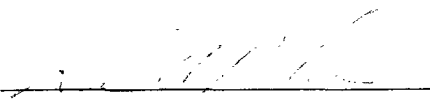
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Abstract

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DEVELOPMENT AND CHARACTERIZATION OF A METHODOLOGY FOR THE SIMULTANEOUS AND INDIVIDUAL DETERMINATION OF IN VIVO RECEPTOR OCCUPANCY AT MU, DELTA, AND KAPPA OPIOID RECEPTORS, AND EXAMINATION OF THE EFFECTS OF OPIOID ANTAGONIST OCCUPANCY ON FEEDING BEHAVIOR IN THE RAT

The World Health Organization considers obesity to be a global epidemic. While changes in diet and exercise have been effective in reversing obesity in some individuals, most such attempts fail to result in sustained weight loss. Current pharmacological treatments are only marginally effective. Opioid receptor antagonism has been shown to decrease food intake in multiple clinical and preclinical models. A thorough understanding of the opioid receptor subtype specific contributions to these effects could potentially aid in the development of novel treatments with diminished side effect liability. Such an understanding has been complicated by the fact that prior investigations included no direct measurement of receptor occupancy to confirm the presumed selectivity. In the present study, LY255582, a particularly potent and long lasting pan opioid antagonist, was examined for its effects in decreasing intake by rats of a highly palatable diet during a one hour scheduled exposure. The receptor subtype specific contributions to the observed effects were examined using a recently reported mass spectrometry (MS) based receptor occupancy technique. Unlike conventional

occupancy methods, this technique does not use radiolabeled ligands and allows for the simultaneous measurement of occupancy at each of the three opioid receptor subtypes (mu, delta, and kappa) in vivo. Subtype specific effects of opioid antagonism in this feeding paradigm were further explored with putatively selective opioid antagonists, with subsequent confirmation of the desired receptor selectivity. MS based occupancy methods specific for determining opioid subtype receptor occupancy had not been reported previously, so this work includes the development and validation of these methods. The conclusions drawn from this investigation include that occupancy of mu receptors is responsible for the effects seen with LY255582 and the mu selective antagonist, cyprodime. Antagonist occupancy of delta receptors has no effect in this feeding paradigm. Selective occupancy of kappa receptors may be effective when occupancy of this receptor approaches 70%.

Jay R. Simon Ph.D. – Chair

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