EFFECT OF N-ACYLETHANOLAMINE ACID AMIDASE INHIBITION ON MESOLIMBIC DOPAMINE AND LOCUS COERULEUS NORADRENERGIC NEURONAL RESPONSES TO MORPHINE

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Morphine is a potent opioid analgesic used to alleviate moderate or severe pain. Nowadays, opioid prescriptions are restricted due to the development of tolerance and the risk to develop addiction. Dopaminergic ventral tegmental area (VTA) and noradrenergic locus coeruleus (LC) are two crucial brain areas that play a pivotal role in addiction. In fact, VTA is important for the acquisition phase, since it is the main actor mediating rewarding properties of opioids. On the other hand, LC is a key component that contributes to the development of withdrawal symptoms.

Emerging evidence suggests that N-palmitoylethanolamine (PEA), an endogenous lipid neuromodulator, delays the development of morphine tolerance. In fact, it has been shown that PEA administration in morphine treated rats prolongs morphine's efficacy as analgesic. An alternative indirect way to increase endogenous PEA bioavailability is the inhibition of N-acylethanolamine acid amidase (NAAA), one of its major hydrolyzing enzymes. Thus, the aim of this study is to assess whether increasing endogenous brain PEA levels is capable to modulate neurophysiological response to morphine.

Therefore, our strategy was to augment endogenous PEA levels through a novel specific brain permeable NAAA inhibitor, AM11095. Then, we employed *in vivo* electrophysiology recordings in anaesthetized adult male rats that we treated with AM11095(15mg/kg, i.p.) or with its vehicle. After 30 minutes from drug administration, we assessed the electrophysiological response to morphine of VTA dopamine cells (cumulative doses 0.5-4.0 mg/kg, i.v.) and LC noradrenergic cells (cumulative doses 0.125-2.0 mg/kg, i.v.).

While preliminary, our results indicate that administration of AM11095: a) does not significantly affect basal electrophysiological properties of VTA DA neurons nor LC NA neurons, and b) does not alter their excitatory or inhibitory response, respectively, to morphine administration. Our next step is to unveil whether increasing endogenous PEA levels in the brain modulates morphine's effects on neuronal responses to nociceptive stimuli or attenuates the development of dependence following chronic morphine administration.