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A Novel Role of Submedius Thalamus and its Projections to Orbitofrontal Cortex in Incubation of Oxycodone Craving After Forced Abstinence

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Oxycodone seeking progressively increases during abstinence and maintains for an extended period in rats, a phenomenon termed incubation of oxycodone craving. We previously found that the orbitofrontal cortex (OFC) plays a causal role in this incubation after forced abstinence. Here, we aimed to identify critical upstream regions of OFC in incubation of oxycodone craving by focusing on the submedius thalamus (Sub), a poorly understood thalamic area. In Exp. 1, rats received 10 days of oxycodone self-administration training. We injected a mixture of muscimol + baclofen (3 + 20 ng/ 0.3 μ l/side) into Sub 15 min before the oxycodone-seeking test on abstinence day 15. We found that pharmacological inactivation of Sub decreased incubated oxycodone seeking. In Exp.2, we first injected fluorescence-conjugated cholera toxin subunit B (CTb-488) ipsilaterally into OFC and trained rats for oxycodone self-administration. On abstinence day 15, we either tested (Seeking-test) or did not test (No-test) rats for oxycodone seeking. Immediately after the test, we perfused the rats for immunohistochemistry to label Fos (a neural activity marker) in Sub. We found that the number of Fos + CTb double-labeled cells in Sub was significantly higher in Seeking-test group than No-test group on abstinence day 15. Taken together, our data showed that Sub played a critical role in incubated oxycodone seeking, and the activation of Sub \rightarrow OFC projections was associated with oxycodone seeking on abstinence day 15. Ongoing studies are using the chemogenetic approach to study the role of Sub to OFC projections in incubation of oxycodone craving after forced abstinence.