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Development of an iPSC-preBötC neuron opiate overdose and recovery multi-organ platform

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Opioid overdose is the leading cause of their lethality, posing an urgent need to new platforms and assays. The key brain region involved in opioid-induced respiratory depression (ORID) is the preBötzinger Complex (preBötC) and current knowledge has mainly been obtained from animal systems. This study aimed to establish a human-based opioid overdose model using preBötC neurons derived from human induced pluripotent stem cells (hiPSCs). A de novo protocol was developed for differentiating preBötC neurons from hiPSCs. These neurons express essential preBötC markers analyzed by immunocytochemistry and demonstrate expected functional features as analyzed by patch clamp electrophysiology. Furthermore, the dose-dependent inhibition of these neurons' activity was demonstrated for four different opioids (DAMGO, fentanyl, methadone, codeine), with identified IC_{50}'s comparable to the literature. Moreover, inhibition by all the four tested opioids was rescued by naloxone in a concentration-dependent manner. To investigate the opioid drug efficacy and off-target toxicity, the preBötC model was established on microelectrode array and integrated into a 5-organ microfluidic system containing preBötC neurons, hepatocytes, cardiomyocytes, skeletal muscle and kidney renal proximal tubule cells, in which the opioid overdose effect and its recovery by naloxone was reproduced as well as functional toxicities of the other organ models. The iPSC-preBötC model is a crucial step for investigating ORID and combating the overdose crisis. Its integration into the multi-organ system provides a powerful platform for evaluating the genetics and epigenetics of substance abuse disorders as well as the drug efficacy for therapy development. (Supported by NIH 1UG3TR003081)