POPULATION: To achieve the objective, we evaluated mice with pancreas lineage Kras-mutation (KC mice), which are predisposed to develop the full spectrum of pancreas cancer precursor lesions (pancreatic intra-epithelial neoplasia or PANIN-1, 2, 3) and PDAC. We subjected KC mice to a light-dark phase shift protocol known to induce circadian disruption (KCCD, n = 18), and another group to standard lighting conditions (KCNC, n = 31), with equal numbers of males and females in each group. The mice were allowed access to food and water ad libitum until sacrifice at age 9 months. Histopathologic evaluation of the pancreas was then performed to assess for pancreatic inflammation, pancreatic precursor lesions (PANIN) and PDAC. Fisher's Exact Test was used to evaluate differences in incidence. RESULTS/ANTICIPATED RESULTS: As expected, both groups of mice demonstrated 100% incidence of chronic pancreatitis and PANIN-1 (low-grade precursor lesion) at age 9 months. This is consistent with the KC phenotype. However, the KCCD mice demonstrated a significant increase in acute pancreatic inflammation (61.1% vs 19.4%, $p = 0.005$) compared to KCNC mice. Furthermore, intermediate grade precursor lesions (PANIN-2) were also significantly increase in the KCCD mice (38.9% vs 6.5%, $p = 0.006$). Incidence of high-grade precursor lesions (PANIN-3, or carcinoma in situ: 22.2% vs 9.7%) and PDAC (27% vs 19%) were also increased, but these were not statistically significant. These results are notable given the established progression from higher grade premalignant PANIN lesions (PANIN-2, PANIN-3) to PDAC. DISCUSSION/SIGNIFICANCE OF FINDINGS: Insight into how circadian disruption leads to increased PANIN-2 formation and increase in acute inflammation may be advantageous for understanding circadian disruption in PDAC carcinogenesis. The circadian clock is present in immune cells and disruption can induce immune dysregulation. This mechanism will be evaluated in follow up studies.

15727

K_{ATP} channel prodrugs as therapeutics for chronic pain and substance abuse disorders

Alexis Doucette, Kayla Johnson, Peter I. Dosa and Amanda H Klein
University of Minnesota

ABSTRACT IMPACT: Pharmacological activation of K_{ATP} channels may provide analgesia and attenuate opioid tolerance and withdrawal OBJECTIVES/GOALS: Our long term goal is to develop therapeutics for the treatment of the overuse of opioids. The objective of this application is to test novel K_{ATP} channel-targeting prodrugs in rodent models of neuropathic and inflammatory pain in addition to opioid tolerance after chronic morphine administration. METHODS/STUDY POPULATION: In one study, two different measures for chronic pain were implemented in mice. Male and female mice (n=10) were subjected to spinal nerve ligation (SNL) or intraplantar injection of Complete Freund's Adjuvant (CFA) to induce neuropathic and inflammatory pain, respectively. Administration of K_{ATP} channel prodrugs (60ug, it) attenuated mechanical hypersensitivity after SNL or CFA compared to vehicle (saline). In a separate study, changes in mechanical hypersensitivity were tested while mice undergo chronic morphine treatment (15mg/kg, 2x, 5 days) with administration of the prodrugs. Tolerance was measured as the loss of antinociception, and withdrawal is measured ~24 hours after the final morphine injection. RESULTS/ANTICIPATED RESULTS: Intrathecal administration of either K_{ATP} channel prodrugs significantly attenuated mechanical hypersensitivity after SNL and significantly attenuated mechanical hypersensitivity after CFA in mice. We predict that intrathecal administration of these prodrugs will also attenuate morphine tolerance and withdrawal in mice. This hypothesis is based off our previous data indicating non-water soluble K_{ATP} channel agonists produce analgesia and attenuate morphine tolerance in mice. DISCUSSION/SIGNIFICANCE OF FINDINGS: Pharmaceutical strategies to utilize K_{ATP} channels for therapeutics have been hindered due to the low solubility and low ability to cross the neurovascular unit. Newly developed, water-soluble K_{ATP} channel openers could be useful pharmaceutical strategy to reduce chronic pain, opioid tolerance, and withdrawal in human populations.

19233

Basis profile curve identification to understand electrical stimulation effects in human brain networks

Kai J. Miller, Klaus-Robert Muller and Dora Hermes
[1]Mayo Clinic and [2]Google Brain, Berlin

ABSTRACT IMPACT: Brain networks can be explored by delivering brief pulses of electrical current in one area while measuring responses in other areas, and this describes an open-source novel algorithm to carry out this exploration. OBJECTIVES/GOALS: If we focus on a single brain site and observe the average effect of stimulating each of many other brain sites, visually-apparent motifs in the temporal response shape emerge from adjacent stimulation sites. There are no existing approaches to identify and quantify the spatiotemporal structure of these motifs. METHODS/STUDY POPULATION: Individual stimulation trials are correlated with one another, then a correlation-significance matrix quantifying similarity between stimulation sites is decomposed with non-negative matrix factorization, in which the inner dimension is iteratively reduced. The dimensionality reduction identifies stimulation sites that produce a common elicited temporal response, and linear kernel PCA is applied to obtain the robust profile of this response cluster. RESULTS/ANTICIPATED RESULTS: We describe and illustrate a data-driven approach to determine characteristic spatiotemporal structure in these response shapes, summarized by a set of unique 'basis profile curves' (BPCs). Each BPC may be mapped back to underlying anatomy in a natural way, quantifying projection strength from each stimulation site using simple metrics. Our technique is demonstrated for an array of implanted brain surface electrodes in a human patient, and our code is shared at https://purl.stanford.edu/rc201dv0636. DISCUSSION/SIGNIFICANCE OF FINDINGS: This framework enables straightforward interpretation of single-pulse brain stimulation data, and can be applied generically to explore the diverse milieu of interactions that comprise the connectome.

19734

L-type calcium channels in cerebellar neuron development and motor learning

DeAnna O'Quinn, *Aislinn Williams, Ashley Parker, Bryn Myers, Ashley Plumb, Hsiang Wen and Marisol Lauffer
University of Iowa Institute for Clinical and Translational Science

ABSTRACT IMPACT: We aim to understand how LTCCs impact cerebellar function. OBJECTIVES/GOALS: L-type calcium channels

https://doi.org/10.1017/cts.2021.423 Published online by Cambridge University Press