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Presenilins: A novel class of calcium modulators

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Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5 mi Americans. As such, AD poses a significant burden on the affected individual, caregivers and society. Most cases of AD are attributed to the sporadic form, which is believed to be of multifactorial origin. However, several genetic loci etiological for the rare familial form of the disease have been identified. One of the loci is the group of presenilin proteins, which form the enzymatic core of the γ-secretase complex. Most of the almost 200 identified familial AD mutations in presenilins are located in the gene encoding presenilin-1, while presenilin-2 mutations typically cause later onset familial AD. Recent evidence identified the group of presenilin proteins as potent modulators of intracellular calcium signaling, through potentiation of the intracellular ryanodine receptor, which likely underlies this phenomenon. This potentiation occurs via the highly evolutionarily conserved N-terminal region of presenilin, resulting in differential modulation of the ryanodine receptor by presenilin-1 and presenilin-2. The proposed mechanism is in accordance with previous studies identifying elevated Ca^{2+} concentrations in the endoplasmic reticulum during AD, and the critical role of ryanodine receptors in regulating calcium via calcium-induced calcium release. Furthermore, ryanodine receptors contribute to the pathologic, elevated intracellular Ca^{2+} concentrations observed in AD. Intriguingly, similar Ca2+ dyshomeostasis occurs during healthy aging, in the absence of known mutations. Utilizing preclinical models for healthy aging, we have implicated presenilin proteins in the etiology of age-related changes in synaptic signaling and, ultimately, age-related deficits in memory and motor coordination. In this keynote talk, the author will summarize the evidence for the group of presenilin proteins as a novel class of calcium modulators, and discuss the opportunities for targeting presenilin proteins as novel drug targets for age-related and neurodegenerative diseases, incl. AD.

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Rapid Intermittent Deep Brain Stimulation Biases Behavior in Financial Decision-Making Task

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We report single-unit responses recorded from the human subthalamic nucleus (STN) in patients undergoing deep brain stimulation while engaged in a financial decision-making task. The task is modeled as a simplified version of the classic card game "war". The subject is dealt a card and asked to make a high or low wager ($5 or $20). Immediately following their choice they are shown their opponent's card––the player with the highest card wins. We recorded 20 individual neurons from 5 patients. We found that during the go-cue period, neuronal activity in the STN predicted whether the subject would ultimately bet high or low on trials where the probability of a positive or negative outcome were equal (6-card trials, two-tailed t-test, $p = 0.03$). To explore this further, we used intermittent electrical stimulation to assess changes in financial decision-making. Using modified stimulator we applied one of three stimulation conditions during 6-card trials: no stimulation, 1 sec of stimulation at the fixation, or 1 sec of stimulation at the go-cue epoch. We found that intermittent stimulation at the go-cue epoch––the same period STN neurons encode the upcoming decision––biases subject to make a low wager (binomial proportion, 95% c.i.). Fixation and no stimulation categories had no effect on decision-making. In this study, we demonstrated that neuronal activity in the dorsal STN predicts financial decisions. We then showed that we could apply intermittent electrical stimulation through the implanted electrode to bias the decision signal and ultimately alter the subject's behavior.

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