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Presenilins: A novel class of calcium modulators

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5 million 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 Ca^{2+} dyshomeostasis occur 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.

Biography

Simon Kaja is an experienced neurobiologist with a long-standing research track record in academia the biotech and pharmaceutical industry. He currently serves as an Associate Director of Preclinical Research at the Vision Research Center at the University of Missouri - Kansas City, School of Medicine. He is the Director of Microscopy of the imaging core facility at the Vision Research Center and also holds a post of Assistant Professor of Ophthalmology. His NIH-funded research program focuses on human neurological and neurodegenerative diseases, visual disorders and inflammation. He obtained his BSc (Hons.) degree in Molecular Biology and Biochemistry from Durham University, UK and holds a PhD degree in Medicine/Neuroscience from Leiden University, Netherlands. Prior to joining the faculty at the University of Missouri - Kansas City, he has performed Postdoctoral work at The University of British Columbia (Vancouver, B.C., Canada) and the University of North Texas Health Science Center (Fort Worth, TX). In addition to his academic work, he has worked and was consulted by a number of pharmaceutical companies, incl. Novo Nordisk A/S, Bayer AG, Neuromed Pharmaceuticals Inc., and NeuroSearch A/S. He is CEO and co-founder of K&P Scientific LLC, a scientific consulting company headquartered in Kansas City, MO.

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