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Review

Calcium channelopathies and Alzheimer's disease: Insight into therapeutic success and failures

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ABSTRACT

Calcium ions are versatile and universal biological signaling factors that regulate numerous cellular processes ranging from cell fertilization, to neuronal plasticity that underlies learning and memory, to cell death. For these functions to be properly executed, calcium signaling requires precise regulation, and failure of this regulation may tip the scales from a signal for life to a signal for death. Disruptions in calcium channel function can generate complex multi-system disorders collectively referred to as "calciumopathies" that can target essentially any cell type or organ. In this review, we focus on the multifaceted involvement of calcium signaling in the pathophysiology of Alzheimer's disease (AD), and summarize the various therapeutic options currently available to combat this disease. Detailing the series of disappointing AD clinical trial results on cognitive outcomes, we emphasize the urgency to design alternative therapeutic strategies if synaptic and memory functions are to be preserved. One such approach is to target early calcium channelopathies centrally linked to AD pathogenesis.

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1. Calcium channelopathies and effects on tissue function

One of the most fascinating and versatile signaling factors in the human body is calcium. Calcium signaling lies at the heart of almost everything we do, how we move, how our brains process information and store memories. This critical second messenger regulates physiological systems at multiple levels ranging from gene transcription (Mellstrom and Naranjo, 2001; Watanabe et al., 2006), to membrane potential and excitability (Hagenston et al., 2008; Stutzmann et al., 2006; Verkhratsky, 2002), muscle contraction (Gomez et al., 1997; Jaggar et al., 2000) and synaptic plasticity and memory encoding (Fitzjohn and Collingridge, 2002; Malenka and Bear, 2004; Malenka and Nicoll, 1999; Mulkey and Malenka, 1992). To coordinate this vast array of functions, calcium signals must be flexible yet precisely regulated. It is therefore not surprising that disruption of calcium channel function can result in a host of disorders, collectively termed "calciumopathies". Calciumopathies cover a broad category of conditions that include monogenic as well as complex polygenic diseases such paralysis, malignant hyperthermia, bipolar disorder, autism spectrum disorders and neurodegenerative diseases (Gargus, 2009; Imbrici et al., 2013; Kullmann, 2010).

As a learning tool, calciumopathies can provide valuable insight into the functioning of electrically excitable cells in the brain, skeletal muscle, and heart. A major feature of calcium channelopathies in excitable tissue is a periodic disruption of rhythmic activity which results in a specific functional impairment. For example, in cardiac muscle, this disruption produces a fatal arrhythmia due to delayed

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repolarization of the cardiac myocytes following a heartbeat, a condition known as long QT syndrome. Normally, the myocardium repolarizes and relaxes in preparation for its next synchronous depolarization that allows it to contract and pump blood into major arteries. Impaired repolarization causes loss of synchrony and pumping fails, resulting in arrhythmia (Goldenberg and Moss, 2008; Priori and Napolitano, 2006). In skeletal muscle, aberrant calcium channel function causes periodic alterations in contractility ranging from paralysis to rigidity, myotonia and malignant hyperthermia. Hypokalemic periodic paralysis, which presents as episodic muscle weakness accompanied by low serum potassium levels, is caused by mutations in the voltage sensing segments of the α1 subunit of L-type voltage-gated calcium channels (Jurkat-Rott et al., 1994; Ptacek et al., 1994). Malignant hyperthermia results from mutations in the type 1 ryanodine receptor, the ryanodine receptor isoform in skeletal muscle which underlies excitation–contraction coupling and muscle contraction. Malignant hyperthermia is triggered by volatile anesthesia leading to excessive type 1 ryanodine receptor calcium release and subsequent muscle rigidity, followed by acidosis, hypercapnea (increased blood carbon dioxide), hypoxemia (decrease in blood oxygen) and hyperthermia (Iles et al., 1994; Monnier et al., 1997; Otsu et al., 1994).

In the central nervous system, disturbances in rhythmic activity can generate seizure activity (episodic, synchronous electrical discharges), epilepsy (Steinlein, 2008), migraine syndromes, and ataxias (Dodick and Gargus, 2008; Ophoff et al., 1996). Migraine syndromes or familial hemiplegic migraine is characterized by migraines, hemiparesis and cerebellar atrophy and often presents together with episodic ataxia type 2. Episodic ataxia type 2 is characterized by paroxysmal attacks of cerebellar ataxia, vertigo and visual disturbances. Spinocerebellar ataxia type 6 is characterized by progressive and permanent dysfunction of cerebellar afferent and efferent connections resulting in ataxia, dysarthria and occulomotor disorders. These distinct neurological diseases are caused by mutations in the CACNA1A gene that encode the ion-pore and voltage sensor-containing α1 subunit of P/Q-type voltage-gated calcium channels. These three conditions are closely related at the molecular level with some degree of phenotypic overlap. However, what aspect of channel function is critical to these phenotypes and whether it involves a gain or loss of function is still somewhat controversial (Pietrobon, 2010; Rajakulendran et al., 2012; Romaniello et al., 2010). Mutations in the CACNA1C gene, which encodes the α1 subunit of L-type voltage-gated calcium channels, causes Timothy Syndrome, a multisystem disorder characterized by congenital heart disease, lethal arrhythmias, immune deficiency, hypoglycemia, cognitive abnormalities and autism (Splawski et al., 2004). This missense mutation (G406R) generates a constitutively active inward calcium current due to loss of voltage-dependent inactivation. The list of neurological conditions associated with calcium channel dysfunction continues to expand, and also includes schizophrenia ($Ca_v1.2$ L-type calcium channel) (Tesli et al., 2013; The-International-Schizophrenia-Consortium, 2009), autism spectrum disorder ($Ca_v1.2$ L-type calcium channel, $Ca_v3.1$ T-type calcium channel, $Ca_v3.3$ T-type calcium channel) (Lu et al., 2012), bipolar disorder ($Ca_v1.2$ L-type calcium channel) (Green et al., 2010; Tesli et al., 2013), Parkinson's disease ($Ca_v1.3$ L-type calcium channel) (Ilijic et al., 2011; Schapira, 2013), Huntington's disease(inositol triphosphate receptor, ryanodine receptor, transient receptor potential cation channel type 1, store operated calcium channel) (Bezprozvanny, 2011; Wu et al., 2011), and Alzheimer's disease (N-methyl-D-aspartate/NMDA receptor, metabotropic glutamate receptor, inositol triphosphate receptor, ryanodine receptor, and calcium sensing receptor) (Armato et al., 2013; Foskett, 2010; LaFerla, 2002; Popugaeva and Bezprozvanny, 2013; Stutzmann et al., 2007; Um et al., 2013), among others. Here, we focus on the contribution of calcium channel dysfunction in AD, and the rationale for targeting calcium channels as a therapeutic strategy in light of the recent failed clinical trials targeting amyloid processing.

2. Alzheimer's disease as a calciumopathy

The etiology of AD is unknown, yet increasing evidence points to altered calcium homeostasis as an early and sustained cellular disease mechanism. While there are many diagnostic features, genetic mutations, and risk factors associated with AD, calcium dysregulation is the common denominator associated with many of them (Berridge, 2013; Bezprozvanny and Mattson, 2008; Chakroborty and Stutzmann, 2011; Stutzmann et al., 2007); and in many cases, precedes the detectable pathology (Chakroborty et al., 2009; Cheung et al., 2010; Chong et al., 2011; Muller et al., 2011; Pratt et al., 2011; Stutzmann et al., 2006; Zhang et al., 2009). As listed above, several channels are implicated in the calcium dyshomeostasis associated with AD (Fig. 1). Two of the most studied are localized to the endoplasmic reticulum (ER), the intracellular repository whose calcium levels are several orders of magnitude greater than the surrounding cytosol: the ryanodine receptor and inositol triphosphate receptors. These channels are highly expressed in cortical and hippocampal brain regions which support learning and memory functions and are also vulnerable to AD pathology (Hertle and Yeckel, 2007; Morrison and Hof, 2002). The inositol triphosphate receptors are activated by the second messenger inositol triphosphate, whereas the ryanodine receptor is triggered by cytosolic calcium. The activation of these channels is amplified by the phenomenon of calcium-induced calcium release (CICR), a regenerative mechanism by which calcium enhances its own release from inositol triphosphate and ryanodine receptors (Finch et al., 1991; Friel and Tsien, 1992). Long term synaptic plasticity, the cellular correlate of learning and memory (Martin et al., 2000; Whitlock et al., 2006), is also modulated by ER calcium signaling (Bardo et al., 2006; Fitzjohn and Collingridge, 2002; Park et al., 2008). The link between ryanodine receptor-evoked calcium signaling and memory encoding has been demonstrated in many studies, and show that altered ryanodine receptor function (type 2 and type 3 ryanodine receptors in particular) disrupts synaptic transmission, long term plasticity, and memory performance (Adasme et al., 2011; Baker et al., 2013; Balschun et al., 1999; Fujii et al., 2000; Futatsugi et al., 1999; Oules et al., 2012; Peng et al., 2012). Thus, there is a strong association between impairments in ER calcium signaling and impaired memory functions in AD.

The connection between altered calcium signaling and AD is well-documented for both the more prevalent sporadic classification, and the dominantly inherited familiar form (Familial AD) caused by mutations in amyloid precursor protein (APP) or presenilin 1 or 2 genes (PS1, PS2). While the cause of sporadic AD is unknown, the recognized risk factors and diagnostic features can each be linked to neuronal calcium signaling aberrations. Foremost among the genetic risk factors is ApoE4 (Apolipoprotein E4) allele expression, which generates altered calcium responses by via a cell-surface LDL (low-density lipoprotein) receptor-mediated mechanism that recruits plasma membrane calcium channels like the NMDA receptors and voltage-gated calcium channels. This in turn triggers further intracellular calcium release and contributes to synaptic signaling disruptions and cell death (Ohkubo et al., 2001; Tolar et al., 1999). An additional AD risk factor that is moving to the forefront in terms of awareness and prevention is the occurrence of a previous traumatic brain injury (Gentleman et al., 1993; Johnson et al., 2010; Shively et al., 2012). After a traumatic brain injury, there is an acute phase of calcium dyshomeostasis due to cellular responses to injury which includes glutamatergic excitotoxicity and lasts minutes