Revelations from a bicistronic calcium channel gene

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The voltage-gated calcium channel (VGCC), CACNA1A, is associated with several neurological disorders, including familial hemiplegic migraine, episodic ataxia type 2, epilepsy, and spinocerebellar ataxia type 6 (SCA6).¹ CACNA1A encodes the Cav2.1 (α1A) subunit, the main pore-forming subunit of the P/Q-type VGCC, responsible for the Ca²⁺ currents that mediate transmitter release in many CNS synapses. CACNA1A contains a CAG repeat in exon 47 that encodes the polyglutamine (polyQ) tract, which is expanded in SCA6. Until recently the prevailing hypothesis was that SCA6 was due to the presence of the expanded polyQ tract in the C terminus of a long splice variant of α1A, which perturbed channel function.² However, studies attempting to implicate altered channel function in SCA6 have yielded conflicting findings.

Recently, we reported that a 75 kDa C-terminal “fragment” of α1A (α1ACT) containing the polyQ tract forms a stable polypeptide, enriched in nuclear fractions in cerebellum, that acts as a transcription factor for neuronally expressed genes. α1ACT enhances the expression of at least 3 genes, GRN, PMCA2, and BTG1, in pheochromocytoma cells (PC12) and cerebellar tissue, potentiates NGF-mediated neurite outgrowth in PC12 and cerebellar tissue, potentiates NGF-mediated neurite outgrowth in PC12 as well as primary rat granule neurons, with the highest activity of F-Luc seen in neuronal cell lines PC12 and SY5Y. These latter levels in neuronal cells were 1.8- to 2-fold greater, respectively, than in HEK 293 cells derived from human kidney cells. This observation suggests that certain neuron-specific cellular factors may influence the activity of the CACNA1A IRES. Taken together, these data further indicate that the CACNA1A gene contains a functional cellular IRES that mediates the expression of the second gene product, α1ACT, of the CACNA1A gene (Fig. 1).

There are currently only a few other genes known, namely PITSLRE/CDK11, USP18-sf, Cx43, Cx55.5, and Notch2, in which IRES elements found in the coding region, rather than in the 5′-UTR of the mRNA, initiate translation of smaller proteins at alternate start codons.⁶ ⁷ We speculate that the presence of IRES elements in the coding region of cellular genes leading to the separate expression of C-terminal domains has important biological implications. Several proteins encoded by these “second cistrons” are novel isoforms or N-terminally truncated proteins, some of which enter the nucleus and possibly function as transcription factors. These
Figure 1. Schematic illustration of expression regulation and function of α1A and α1ACT. The CACNA1A gene, encoding the VGCC subunit α1A, is bicistronic. The second gene product, α1ACT, is generated from the α1A transcript by a cellular IRES located within the coding region of the α1A mRNA. α1ACT is a transcription factor that regulates expression of several neuronally-expressed genes, promoting neurite outgrowth. The α1ACT_{SCA6} reduces viability of cells and causes cerebellar cortical atrophy in an animal model.