Select putative neurodevelopmental toxins modify SNAP-25 expression in primary cultures of rat cerebellar granule cells

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A B S T R A C T

A presynaptic protein SNAP-25 belonging to SNARE complex which is instrumental in intracellular vesicular trafficking and exocytosis, has been implicated in hyperactivity and cognitive abilities in some neuropsychiatric disorders. The unclear etiology of the behavior disrupting neurodevelopmental disabilities in addition to genetic causes most likely involves environmental factors. The aim of this in vitro study was to test if various suspected developmental neurotoxins can alter SNAP-25 mRNA and protein expression in neurons. Real-time PCR and Western blotting analyses were used to assess SNAP-25 mRNA and protein levels in primary cultures of rat cerebellar granule cells (CGCs). The test substances: tetrabromobisphenol-A (TBBPA), thimerosal (TH), silver nanoparticles (NAg), valproic acid (VPA) and thalidomide (THAL), were administered to CGC cultures at subtoxic concentrations for 24 h. The results demonstrated that SNAP-25 mRNA levels were increased by 49 and 66% by TBBPA and THAL, respectively, whereas VPA and NAg reduced these levels to 48 and 64% of the control, respectively. The SNAP-25 protein content in CGCs was increased by 79% by TBBPA, 25% by THAL and 21% by NAg; VPA and TH reduced these levels to 73 and 69% of the control, respectively. The variety of changes in SNAP-25 expression on mRNA and protein level suggests the diversity of the mechanism of action of the test substances. This initial study provided no data on concentration-effect relations and on functional changes in CGCs. However it is the first to demonstrate the effect of different compounds that are suspected of causing neurodevelopmental disabilities on SNAP-25 expression. These results suggest that this protein may be a common target for not only inherited but also environmental modifications linked to behavioral deficits in neurodevelopmental disabilities.

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1. Introduction

The synaptosomal-associated protein 25 (SNAP-25) belongs to the evolutionarily conserved SNARE protein complex present in presynaptic and vesicular membranes; this complex is responsible for the intracellular vesicular trafficking and the regulation of exocytosis in eukaryotic cells (Jena, 2011; Cupertino et al., 2016). In neurons SNAPARE proteins are involved in the release of neurotransmitters and growth of plasma membrane. SNAP-25 is a multifunctional protein. This protein is required for sprouting and elongation of neurons (Osen-Sand et al., 1993; Kimura et al., 2003), plays a role in synaptogenesis (Oyler et al., 1991), is also instrumental in the recycling of the membranous proteins (Peng et al., 2013). In concert with other SNARE proteins SNAP-25 contributes to neurotransmitter release (Rizo and Xu, 2015), and modulates the activities of voltage-gated calcium channels (Matteoli et al., 2009). Its key role in cognitive functions (Gosso et al., 2006; Hou et al., 2006) and regulation of locomotor activity in vivo has been recognized (Hess et al., 1996).

It has been suggested, that the SNARE complex may play an important and diversified role in developmental disabilities (Cupertino et al., 2016), and altered expression of SNAP-25 can produce abnormal behavioral phenotypes in schizophrenia (Mukaetova-Ladinska et al., 2002; Thompson et al., 2003; Gray et al., 2010), attention deficit hyperactivity disorder (ADHD) (Guerini et al., 2011; Zhang et al., 2011) and autism-spectrum disorder (ASD) (Ghezzo et al., 2009). Although human genetic studies found no association of SNAP-25 with ASD, associations with behavioral deficits such as hyperactivity and cognitive function has been detected (Gosso et al., 2006; Guerini et al., 2011; Braidà et al., 2015). Experiments using transgenic mouse models also demonstrated that mutations in SNAP-25 result in...