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ACCUMULATION OF STABLE ~35-37KD ΔFOSB ISOFORMS IN THE REWARD SYSTEM OF CHRONIC DRUG ABUSERS: THE KEY FACTOR OF HIGH RELAPSE RATE?

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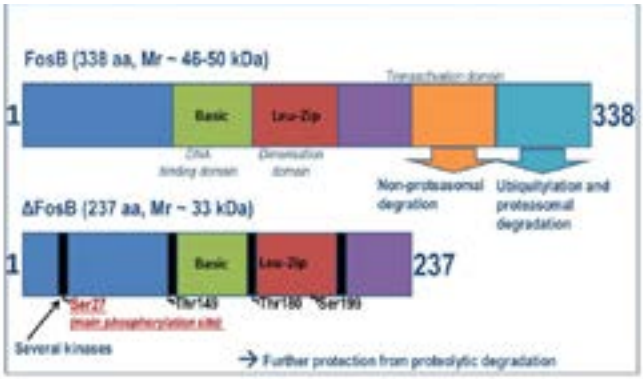
As a member of the Fos family proteins and belonging to the IEGs (Immediate Early Genes), the ~33kD transcription factor ΔFosB, is initiated by a wide range of effects such as drugs of abuse or other psychoactive substances, but also external stimuli of manifold nature. ΔFosB forms heterodimers with Jun proteins, to form active activator protein-1 (AP-1) complexes, binding then to AP-1 sites in the promoter regions of many neural genes. To date, several downstream target genes for ΔFosB have been identified, including NMDAR1, GluR2, Cdk5, and NF-kB, being involved in molecular pathways concerning addictive behavior. Chronically recurring exposures to stimulant interactions induce a displacement of the rather unstable ~33kD transcription factor ΔFosB by highly robust ~35-37kD isoforms; leading to consistent accumulation of these stable ΔFosB derivates particularly in the nucleus accumbens (NAc), a key region in the reward center of the brain, and hippocampus (HPC). These inert ~35-37kD ΔFosB derivatives linger there for several weeks, even after cessation of excitations. A fact seeming to be responsible for the development of sustained neuronal plasticity. Here, we demonstrate the presence of ~35-37kD ΔFosB isoforms in the NAc and HPC of chronic drug abusers via immunoblotting and immunohistochemistry. Moreover, this protein was characterized by means of mass spectrometry to elucidate potential additional phosphorylation sites, seeming to accelerate the factors stability. Our findings provide additional evidence of the potential impact of ΔFosB on its downstream targets, which are responsible for long-term effects and serious adaptations in the brain leading to addictive behavior.

Figure 1: Schematic presentation of full length FosB vs ΔFosB with known phosphorylation sites.



Biography

Monika Heidemarie Seltenhammer completed her DVM and PhD from VMU in Austria and Postdoctoral studies from Veterinary University of Vienna, Max Perutz Laboratories and Medical University of Vienna in Austria, where her core area of scientific work mainly consisted in Cancer Research (melanoma) and Pathology, but also Immunology, Neurology and Virology. She has received several honor and awards. She is a leading member of the scientific staff of Dr. Daniele Ugo Risser at the Department of Forensic Medicine of the Medical University Vienna, where she specializes in Neurobiology and Addiction Behavior.

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