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ACCUMULATION OF HIGHLY STABLE ΔFOSB-ISOFORMS AND ITS TARGETS INSIDE THE REWARD SYSTEM OF CHRONIC DRUG ABUSERS – A SOURCE OF DEPENDENCE-MEMORY AND HIGH RELAPSE RATE?

Background: The ~33kD transcription factor ΔFosB, a Fos-family protein, belonging to the immediate early genes (IEGs), is initiated in the acute phase as a response to a wide range of effects such as drugs, stress, and several external stimuli. ΔFosB forms heterodimers with Jun proteins to generate active activator-protein-1 (AP-1)-complexes. Currently, several downstream target genes for ΔFosB have been identified being involved in molecular pathways concerning addictive behavior, memory and learning. In answer to chronic stimuli, the rather unstable ~33kD transcription factor ΔFosB is replaced by robust ~35-37 kD isoforms due to epigenetic splicing and phosphorylation steps. These highly stable isoforms accumulate in the nucleus accumbens (NAc), a structure close to the hippocampus (HPC), playing a key role within the reward center of the brain. The stabilized ~35-37 kD ΔFosB derivatives linger in the brain for very long time; even beyond cessation of the chronic stimulus. A fact that seems to be responsible for the development of sustained neuronal plasticity, (drug-associated) long-term potentiation (LTP) and memory, and finally high relapse rates.

Method: ΔFosB and cAMP response element binding protein (CREB), brain derived neurotrophic factor (BDNF), JunD, nuclear factor kappa B (NFkB), and cyclin-dependent kinase 5 (Cdk5) in both of the NAc and HPC of deceased chronic human opioid addicts were proven by immunohistochemistry. Immunoblots were positive for accumulated ~35-37 kD ΔFosB isoforms.

Results: All determined proteins showed a significant increased staining pattern in brain samples of chronic drug abusers in comparison non-drug users ($p<0.05$) according to Wilcoxon-Mann-Whitney-U Test. Further, accumulated ~35-37 kD ΔFosB isoforms were detectable in NAc samples of long-term drug addicts by immunoblotting in contrast to the control group, where no trace of any isoform was verifiable ($p<0.05$) according to Wilcoxon-Mann-Whitney-U Test.

Conclusion: Our findings provide additional evidence of the potential strong impact of ΔFosB on its downstream transcriptional targets, which are in turn responsible for sustainable effects and serious adaptations in the brain leading to addictive behavior and dependence memory.

Biography

Monika H. Seltenhammer completed her VMD. and Ph.D. 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. Dr. Monika H. Seltenhammer 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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