

## S24-02 - PHOSPHODIESTERASE 4 (PDE4) VARIANTS: ROLE IN DEPRESSION AND TREATMENT

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cAMP-specific PDE4 are a family of enzymes capable of hydrolyzing cAMP to 5'AMP. cAMP plays a major role in synaptic plasticity, neurite outgrowth, and neuronal differentiation and survival and recent studies demonstrate involvement of cAMP in pathophysiology of depression. The cAMP-specific PDE4 can be differentiated from other PDE families by sequence identity in the catalytic region of the protein and by their ability to be inhibited by a specific class of drugs, of which rolipram is the prototype. PDE4 enzymes are also unique in having 'signature' regions of sequence, called upstream conserved regions (UCR1 and UCR2), located in the N-terminal region of the proteins. There are four PDE4 subfamilies, encoded by separate genes (PDE4A, PDE4B, PDE4C, PDE4D), all are expressed in brain. A few studies suggest that PDE inhibitors show antidepressant-like effects in rodents. To examine the role of PDE4 in depression, we characterized various isoforms of PDE4 in human brain. Expression of PDE4A1, PDE4A4, PDE4A10, PDE4B1, PDE4B2, PDE4B3, PDE4D3, PDE4D4, PDE4D5 and PDE4D9 variants were characterized. All, except PDE4A10, PDE4B1, PDE4D4 or PDE4D5 variants, were highly expressed in human brain. When compared, we found that expression levels of PDE4A1, DE4B2, and PDE4A4 were decreased in PFC and hippocampus of depressed subjects, whereas, no change was observed in expression of PDEB3, PDE4D9, and PDED3 variants. Our study for the first time provides evidence of variant specific alterations in PDE4 in brain of depressed subjects and indicates that these variants may be used as site-specific therapeutic target(s) to develop novel antidepressants.