

S58-4 Pituitary adenylate cyclase-activating polypeptide (PACAP): A new pathway implicated in neuropsychiatric disorders

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PACAP (pituitary adenylate cyclase-activating polypeptide) is a neuropeptide with activities such as neurotransmission, neural plasticity, and neurotrophic actions. Mice lacking PACAP (PACAP^{-/-}) displayed neuropsychological abnormalities, including novelty-induced hyperactivity, sensorimotor gating deficits, and impaired hippocampal memory retention. Most of these abnormalities were amenable to treatment of the atypical antipsychotic risperidone, however, the typical antipsychotic haloperidol showed only limited effects. PACAP^{-/-} mice also showed depression-like behavior, which was again ameliorated by risperidone. In addition, a genetic association study provided evidence that genetic variants in the PACAP gene and its receptor, the PAC₁ receptor gene, were associated with schizophrenia, at least in Japanese population. Further, the overrepresented allele of the PACAP gene SNP in schizophrenia was associated with poorer visual memory performance and reduced hippocampal volume in schizophrenia. These observations taken together suggest that the PACAP and PAC₁ receptor genotypes, and an altered PACAP signaling system could be of relevance in the pathogenesis of schizophrenia. Since PACAP is known to have pleiotropic actions, e.g. modulation of various signaling systems such as dopamine, serotonin and NMDA receptor-mediated signaling systems, it is plausible that PACAP is part of a common genetic etiology shared by mental disorders, and that PACAP signaling or its related signaling pathways may be a target candidate for new therapies.