Blanka Zelezna et al., Endocrinol Metab Synd 2014, 3:2
http://dx.doi.org/10.4172/2161-1017.S1.006

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Endocrinology
October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

Lipidized analogs of prolactin releasing peptide exhibit central effects after peripheral administration

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Prolactin releasing peptide (PrRP) is an anorexigenic neuropeptide produced and acting in the brain. We hypothesized that modification of PrRP by fatty acids will produce PrRP analogs not only more stable but also able to cross the blood brain barrier and therefore applicable by a peripheral administration. PrRP analogs with N-terminal amino group modified with fatty acids of various chain length were synthetized and tested for their binding affinity to pituitary RC-4B/C cells that express PrRP receptor, for their acute central effects on food intake in rodents and possible stimulation of neuronal activity via early gene product Fos in brain areas regulating food intake. Lipidization did not attenuate but rather enhanced binding affinity of PrRP analogs to RC-4B/C cells compared to the native PrRP. Lipidized PrRP analogs containing fatty acids of 14-18 carbons exhibited significant anorexigenic effect after peripheral injection and activated Fos in paraventricular nucleus, arcuate nucleus, and nucleus tractus solitarii while analogs with shorter fatty acids and native PrRP did not. In conclusion, lipidization of PrRP with a longer chain fatty acids (14-18 carbons) enabled increase its stability in circulation and mediated central biological effect PrRP after its peripheral administration.

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