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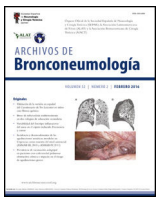

Editorial

Leptin, Orexin, Peptide YY, and Ghrelin Associated With Relapse During Smoking Cessation☆

Relación de la leptina, la orexina, el péptido YY y el ghrelin con la recaída al dejar de fumar

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Nicotine affects the mesolimbic system by binding to neuronal acetylcholine receptors.[1] Available evidence is sufficient to show the involvement of the ventral tegmental area (VTA) and its afferents that project to the nucleus accumbens (NAc) and the prefrontal area (PFA) as a common center that mediates the reward-enhancing effects of nicotine.[2,3] Appetite-regulating peptides, leptin, and orexin, originally involved only in the balance between energy expenditure and craving for food[4] have been shown to act directly on the mesolimbic pathway. Both of these hormones bind to specific receptors located in the dopaminergic neurons of the VTA to stimulate (orexin) or inhibit (leptin) the dopaminergic signal in the NAc.

Leptin

Leptin is a hormone secreted by the adipocytes that contributes to appetite modulation and energy regulation, but it has also been associated with the consumption of psychoactive substances, such as alcohol and nicotine.[4] Leptin modulates the hypothalamic-pituitary-adrenocortical (HPA) axis by weakening the cortisol response to stress, acting presumably at a hypothalamic level. A deregulation in the neuroendocrine stress system, and in the HPA axis in particular, has been associated with various psychiatric disorders, including addiction.[5] Altering the functioning of the HPA axis and attenuating the stress response increases alcohol consumption and the chance of smoking relapse.[5]

Leptin in peripheral blood correlates positively with craving in active smokers.[4] Higher levels of leptin in smokers who have been abstinent for 24 h predict greater craving during smoking cessation, increased withdrawal symptoms, reduced positive affect, greater stress, and more physical symptoms.[5] Two longitudinal studies in successful quitters demonstrated that leptin did not change between time of cessation and 1–3 months after giving up.[6,7] Given this disparity, Potretzke et al.[8] examined the pattern of changes in leptin in response to stress, and its relationship with craving during the initial phase of an attempt to stop smoking. They found that leptin increased with stress, with a positive correlation between leptin and craving, but in contrast, they found no differences in leptin levels between smokers who remained abstinent during 4 weeks and those who relapsed in that period. Lemieux et al.[9] examined leptin levels in men and women, both smokers and non-smokers, to determine its association with psychosocial symptoms and relapse, while they were smoking, and after 48 h and 4 weeks of abstinence. They found that leptin concentrations increased after 48 h of abstinence only in women, and remained stable in non-smokers, in relapsers and in men. They noted that an increase in leptin levels correlated negatively with withdrawal symptoms, which may indicate a protective effect of leptin. Kryfti et al.[10] examined serum changes in leptin, adiponectin, C-reactive protein levels and body mass index in smokers after 3 and 6 months of abstinence, and found that leptin levels increased between the start of abstinence and month 3, and fell between months 3 and 6. Silva Gomes et al.[11] also found that higher concentrations of leptin were associated with increased craving and greater difficulty in achieving abstinence. It has even been shown that 3 months of abstinence produces an increase in weight, a decrease in glycated hemoglobin, and an increase in leptin concentrations, but has no effect on incretins.[12]

Orexin

Orexins are neuropeptides that act as neurotransmitters in the neurons of the lateral hypothalamus.[4] Recent studies have linked orexin with brain regions associated with reinforcement, suggesting that it has a role in addiction.[4] Hollander et al.[13] showed that insular orexin transmission plays a crucial role in the motivational properties of nicotine, and could therefore play an important role in the maintenance of addiction. Orexin directly affects the mesolimbic pathway by binding to specific receptors located in the dopaminergic neurons of the VTA, stimulating the dopamine signal in the NAc. A negative correlation has been found between orexin

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levels and the craving for nicotine in the early stages of abstinence.[4] Orexin and leptin may modulate the reinforcement deficiency in abstinence, increasing nicotine craving.

Other Substances Involved in Nicotine Addiction

An increase in adiponectin[10] (a hormone synthesized in the adipocytes) has been observed in nicotine abstinence, which is, in contrast, reduced in active smokers.[14] Peptide YY (PYY) is an anorexigenic peptide released by the L cells of the gut to reduce energy intake and body weight. Ghrelin is a hormone released into the stomach that is involved in starting and finishing meals.[15] A decrease in ghrelin levels has been associated with successful abstinence, and low levels in the first 24 h to 48 h after abstinence have been associated with a longer time to relapse. PYY has been associated with craving and positive affects on abstinence but not on relapse.[15] Lemieux and al'Absi[15] found increased PYY levels and reduced ghrelin levels in relapsers, but not in abstinent individuals or in non-smokers, so these substances might be useful predictors of relapse, especially in early withdrawal syndrome.

While not all authors agree completely, it has been suggested that leptin levels change in response to stress and could be a good biomarker for craving and difficulty in smoking cessation, and that its role in relapses should be determined. Both PYY and ghrelin have been shown to be useful as predictors of relapse. These initial findings need to be followed up with further studies to clarify these neuroendocrine relationships in nicotine addiction.

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