Role of the Lateral Habenula in modulating the rewarding effects of nicotine

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Tobacco smoking represents a well known risks factor for health. So far, existing smoking cessation therapies have not been proven very successful at quitting this habit and a better understanding of the neurobiology of tobacco dependence is still needed. Nicotine is the neuro-active compound contained in tobacco that is responsible for its rewarding and reinforcing properties by acting on the midbrain dopaminergic system. The lateral habenula (LHb) is an epithalamic structure involved in pain, stress, depression and in encoding aversive stimuli. This structure is known to inhibit the DA system through activation of the RMTg, a GABA-ergic area located caudally to the ventral tegmental area (VTA). The RMTg receives a strong glutamatergic imput from the LHb and is activated by the systemic injection of nicotine in rats. Thus, the LHb might represent a possible target for the action of nicotine. Our data shows that systemic administration of nicotine increases the LHb neuronal activity in vivo in rats. Following nicotine chronic treatment, this response is drastically decreased while after 1 day of withdrawal only low doses of nicotine are able to significantly affect the firing rate of the LHb neurons compared to controls. To further elucidate the role of the LHb in central nicotine effects, we recorded the activity of VTA putative-DA neurons following LHb electrolytic lesion in both drug-naïve and nicotine chronically treated animals. Systemic administration of nicotine induced a significant increase of putative-DA neurons activity. Overall, acute LHb electrolytic lesion did not modify this effect in drug-naïve rats, however, splitting the neurons on the basis of their localization within the VTA, revealed a stronger effect of nicotine on ventro-medial neurons located at the level of the paranigral nucleus. This effect was completely abolished by LHb ipsilateral lesion. Conversely, dorso-lateral neurons, approximately located in the parabrachial pigmented nucleus of the VTA, did respond significantly to nicotine administration only after LHb lesion. Following chronic nicotine treatment, a further acute challenge with nicotine failed to increase VTA putative-DA cells neuronal activity compared to sham-lesioned and control rats. Our evidences strongly suggest that the LHb might play an important role in mediating the effects of nicotine on the midbrain DA system thus participating to the mechanism of addiction to this drug. In conclusion, the LHb might represent a new target for nicotine cessation therapies. Our data suggest that a drug capable of counteracting the decreasing response of the LHb to nicotine following its chronic administration might represent a successful strategy in nicotine addiction.