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Neuropharmacology

Nicotine activates TRPM5-dependent and independent taste pathways

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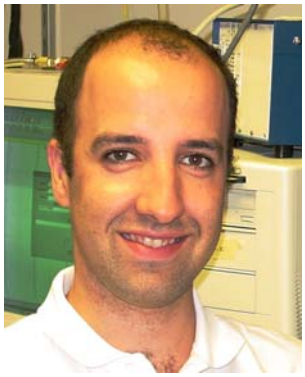

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About the work

Smoking is one the leading causes of preventable mortality and health-related economic burden. It is intimately related to appetitive behaviors with relevant gustatory determinants and, thus, a deeper understanding of gustatory processing, particularly in terms of responses to nicotine, is an important objective in biomedical research.
In fact, nicotine is described as bitter at low concentrations, such as those found in the saliva of smokers. It has also been shown to activate both peripheral taste nerves and taste responsive areas of the brain, such as the insular cortex. In these experiments we used Trpm5 knockout mice that are unable to taste bitter substances, to clarify the effects of nicotine on the taste system. Since these mice do not react to pure bitter substances, such as quinine, we hypothesized that they also would not be able to taste the bitterness of nicotine solutions.
Taste responses to nicotine solutions were measured both in terms of behavioral preference for nicotine solutions and peripheral nerve (chorda tympani) responses to lingual stimulation by nicotine. Surprisingly, responses to nicotine in knockout mice were found to be only partially reduced, but not abolished as was the case for quinine. These findings confirmed the participation of a TRPM5-dependent pathway in taste transduction of nicotine. However, the mice could still sense something, suggesting that there should be an alternate taste pathway in play.
Nicotinic acetylcholine receptors (nAChR) had previously been proposed as taste receptors for nicotine. To explore the role of such receptors, both normal and knockout mice then received mecamylamine, a nicotinic receptor blocker, while behavioral or chorda tympani responses were recorded. Under these conditions, responses to nicotine were inhibited, both in genetically modified and normal mice, demonstrating the existence of an alternate taste pathway for nicotine, that is nAChR-dependent and TRPM5-independent. To further support these findings,

we then used a different approach to show that nAChRs are in fact expressed in taste buds and in the CT nerve.

To verify the relevance of this newly-described pathway for taste guided behavior, an experiment was then conducted in rats to test the effects of mecamylamine. Animals were trained to discriminate between nicotine and quinine solutions, presented at multiple, intensity-paired concentrations in a two-alternative choice paradigm. In this paradigm, the animals could signal if they tasted a quinine solution or a nicotine solution, and they where rewarded when they responded correctly. While the rats responded correctly under baseline conditions, when mecamylamine was added to nicotine, the animals responded as if these solutions tasted more similarly to quinine. This effect was not reproduced when nicotine was replaced by water, thus suggesting that mecamylamine, which inhibits TRPM5-independent pathways, renders the taste of nicotine more similar to that of quinine, a purely TRPM5-dependent tastant.

In other rats, neuronal activity was recorded from populations of neurons in the insular gustatory cortex while the animals consumed nicotine and quinine. We found that activity from the recorded neurons was sufficient for a mathematical model to discriminate between nicotine and quinine. However, consistently with previous findings, when mecamylamine was added to nicotine, neuronal responses to this tastant were rendered similar to those obtained with quinine, further showing that the two taste pathways were being used to guide the rats' behaviors.

Other authors had previously demonstrated the relevance of sensory responses to nicotine in the regulation of smoking-related behaviors. Importantly, increased peripheral sensitivity to bitter tastants was shown to protect from the development of addiction to cigarette smoke, suggesting a role for taste-related processes in the development and regulation of tobacco dependence. In this context, our finding of a nAChR-dependent taste pathway for nicotine was particularly interesting since nAChR-antagonists, which are administered as smoking cessation aids, have an impact on the sensory stimulation by cigarette smoke. We also showed the existence of a previously unknown link between peripheral nAChR-dependent pathways and sensory representation of nicotine in the gustatory cortex. The insular integration of peripheral nicotine taste pathways is also potentially relevant since there is evidence that, in humans, insular lesions may disrupt smoking.

About the author

Albino Jorge Oliveira-Maia graduated in Medicine from the University of Porto in 2002. In 2001 he had received the 'Magalhães Lemos' Prize from the Faculty of Medicine of the University of Porto for excellence in Neurology and Neurosurgery. As a medical student, he also was recipient of a Leonardo da Vinci training grant, allowing part of his clinical training to be completed at Ghent University, in Belgium. In 2002 Albino was accepted into the GABBA graduate program at the University of Porto. He interrupted graduate school for two years to complete pre-specialty post-graduate medical training at Matosinhos Hospital and, in 2005, went back to being a full-time graduate student. Albino graduated in November 2008. His doctoral thesis was developed under the supervision of Dr. Miguel Nicolelis, at Duke University, and Dr. Vasco Galhardo, at the University of Porto. During this period he was recipient of a doctoral fellowship from the Portuguese Foundation for Science and Technology and received travel fellowships from the Gulbenkian Foundation and the Portuguese Society for Neuroscience.

Albino's work has been focused on understanding the neurophysiological and neurochemical correlates of consummatory activity in the central nervous system of awake and freely behaving rodents. He was particularly successful in the use of transgenic mice with taste deficits to clarify issues relating to oral and postingestive multisensory integration and reward processing. During his PhD, Albino authored original manuscripts published in Neuron and PNAS and contributed chapters to two books. He has also presented his work at several international meetings and conferences, both in Europe and the United States. In 2007 he was given a 'Young Investigator Poster Prize' at the European Congress of Obesity and, in 2008, the prize for 'Best Graduate Student Talk' at the Duke Neurobiology Retreat. Currently, Albino is a postdoctoral fellow at the Department of Neurobiology of Duke University Medical Center.