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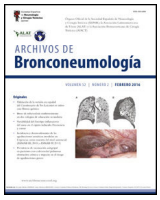

Editorial

Influence of Genes in the Individualization of Smoking Cessation Pharmacological Treatment

According to the World Health Organization (WHO), smoking affects 22.3% of the global population.[1] It is estimated that up to 70% of all smokers want to quit, but only 3–5% of them maintain abstinence after one year.[2] This low success rate encompasses many factors, including a wide variety of behavioral and genetic components. The presence of genetic variants can affect the response to smoking cessation treatments, highlighting the need for an approach that relies more on personalized medicine.

Nicotine is a highly addictive substance. Nicotine binds to heterogeneous nicotinic acetylcholine receptors (nAChR) in the brain. These receptors are also found in neuromuscular junctions and autonomic ganglia.[3] The binding of nicotine at the receptor allows the entry of sodium and calcium, which stimulates the release of dopamine. Dopamine produces a pleasurable experience, which plays a fundamental role in addiction.[2] Besides dopamine, activation of these receptors triggers the release of other substances, such as glutamate, γ-aminobutyric acid (GABA), serotonin, norepinephrine, acetylcholine, and endorphins.[2,3] Glutamate has been related to memory and learning by acting on synaptic plasticity.[3] The release of these neurotransmitters results in reversal of withdrawal symptoms, improved performance, and mood improvement.[2] Dopamine and the other substances mentioned are involved in the positive reinforcing effect experienced by smokers. In addition, the prolonged use of nicotine leads to neuroadaptation, an event that occurs when the number of nAChRs increases, and the receptor is desensitized to the agonist. This fact is believed to be related to nicotine withdrawal symptoms.[2]

Due to the genetic disposition of individuals, nicotine addiction is variable among different populations.[2] Genetic variation in nicotine addiction is mainly determined by the locus on chromosome 15q25.1, with risk alleles increasing nicotine dependence by 30–40%. This locus includes the CHRNA5, CHRNA3, and CHRNB4 genes that encode the nAChRs. These genes contain variants that modify nicotine dependence.[2,4,5] Several meta-analyses based on subjects of European descent have confirmed the association of chromosome region 15q25.1 with cigarette smoking heaviness, defined by cigarettes per day, with the strongest associations reported for the rs16969968 and rs1051730 variants, both of which are highly correlated.[6]

At least two independent signals have been identified in the CHRNA5-A3-B4 region. The first signal is tagged by rs16969968 resulting in alterations in nicotinic receptor conductance in vitro.[6] The rs16969968 variant has been associated with delayed smoking cessation and earlier lung cancer diagnosis.[7] A second signal is tagged by rs680244 and has been related with low mRNA levels of CHRNA5,[2,6] affecting the number of receptors, which could hinder smoking cessation. That is, when smokers decide to quit for the first time, they may experience heightened withdrawal responses in the early phase. This response is due to higher levels of nAChR expression in smokers because of chronic nicotine exposure.[2,8]

On the other hand, neurexins (NRXN; presynaptic cell adhesion proteins), specifically NRXN 1 and 3, are also involved in the development of nicotine dependence and addiction to other substances. Neurexins have been linked to different smoking behaviors. Regarding NRXN1, the rs10865246 variant is associated with greater nicotine addiction. For NRXN3, the rs221497 and rs221473 variants were associated with a lower risk of smoking among Spanish Caucasians.[2]

The way nicotine is metabolized in the body also plays a role in the development and severity of withdrawal symptoms and cravings. The rate at which nicotine is metabolically cleared from the body has important implications for nicotine dependence and the ability to quit smoking.[9] There are several enzymatic pathways involved in nicotine metabolism. Approximately 80% of nicotine is metabolized to cotinine in two phases: the first phase consists of C-oxidation of nicotine to cotinine by CYP2A6 (cytochrome P450, family 2, subfamily A, polypeptide 6) and N′- oxidation to nicotine N′-oxide (NOX) by FMO1, FMO2 and FMO3; and the second phase, nicotine is catalyzed by a cytoplasmic aldehyde oxidase.[2,3] Cotinine is also metabolized to 3-hydroxycotinine (3-HC) by CYP2A6. The remaining 10% of nicotine is metabolized by oxidation, glucuronidation, or methylation before excretion in the urine.[3] About 90% of nicotine and its metabolites are excreted in the urine.[2,3]

Certainly, CYP2A6 variants are critical in nicotine metabolism, as they predict enzymatic activity and the resulting nicotine metabolite ratio levels.[9] The nicotine metabolite ratio (NMR) consists of the 3-hydroxycotinine/cotinine (3HC/COT) ratio and refers to genetic variation in nicotine-metabolizing enzymes and can be used as an indicator of nicotine clearance rate. The NMR has a minimal diurnal variation, its value does not depend on the time the last cigarette was smoked in subjects who smoke at least 5 cigarettes per day.[2,3] The NMR can be measured in saliva, plasma, or serum. Therefore, the NMR can be considered as a predictive biomarker of response to tobacco cessation pharmacotherapy. It is important to know that NMR value can be altered in smokers who use estrogen therapy, pregnant women, obesity, and alcohol consumption.[2]

In a clinical trial in which smokers were randomized to NMR-based treatment, a plasma value of 0.31 was defined.[10] Therefore, subjects who had an NMR < 0.31 were classified as slow nicotine metabolizers, while those who had an NMR > 0.31 were classified as

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fast nicotine metabolizers.[2,10] Faster nicotine metabolizers showed lower quit rates and higher levels of anxiety when were compared to slower metabolizers, a result that has been demonstrated in several studies among Caucasians and African Americans.[11] On the other hand, slow nicotine metabolizers tend to smoke fewer cigarettes per day, and have higher quit rates with nicotine replacement therapy (NRT) and similar quit rates with bupropion.[12] Current best practices suggest that fast nicotine metabolizers will have the best success using varenicline and/or bupropion, while slow nicotine metabolizers will have a greater therapeutic response to NRT.[2,11,12]

DNA methylation analysis also provides significant information about the prevention and cessation of tobacco use. In terms of epigenetic modifications in smokers DNA, it is important to discriminate between two processes: the association between changes in DNA methylation and nicotine dependence, and epigenetic changes as a reflection of tobacco exposure.[13] The most important changes in DNA methylation in response to smoking have been described in the xenobiotic response pathway regulated by the aryl hydrocarbon receptor repressor (AHRR) gene.[13] An interesting fact is that epigenetic modifications in AHRR have also been related to smoking intensity and are reversible after smoking cessation.[13,14]

Nicotine dependence is the result of the interaction between neurobiological, environmental, and genetic factors.[15] Additionally, there are different behavioral factors linked to an individual's predisposition for tobacco use and nicotine addiction, such as anxiety and impulsivity.[2] Identifying these factors provides the opportunity for personalized smoking cessation treatments.

Conflict of interests

The authors state that they have no conflict of interests.

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