Nicotine, atrial fibrosis, and atrial fibrillation: do microRNAs help to clear the smoke?

Andreas Goette*

Department of Internal Medicine, Division of Cardiology, University Hospital Magdeburg, Leipzigerstr. 44, 39120 Magdeburg, Germany

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This editorial refers to ‘Downregulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines’ by H. Shan et al., pp. 465–472, this issue.

Chronic nicotine abuse has clearly been linked to the development and progression of atherosclerosis, myocardial infarction, and heart failure.1 In addition, several studies have also shown that nicotine abuse is associated with the occurrence of cardiac arrhythmias.1–3 The proarrhythmic effect of cigarette smoking seems to depend on the nicotine concentration in the blood.4 Increased nicotine levels raise atrial and ventricular vulnerability to fibrillation.1–4 These profibrillatory effects appear to depend on the inhibition of ion channels and conduction-slowing properties. One factor known to cause a substantial slowing of electrical impulse propagation in cardiac tissue is an increase in the amount of interstitial collagen. Interstitial fibrosis isolates groups of atrial myocytes as well as individual myocytes.4,5 Thus, the development of interstitial fibrosis affects chamber geometry and mechanical performance of the heart and enhances the likelihood of cardiac arrhythmias such as atrial fibrillation (AF). Recently, it was shown that nicotine abuse accelerates atrial collagen accumulation, leading to symptomatic atrial fibrosis at a younger age.6 Experimentally, a linear correlation between nicotine dose and atrial collagen expression was established. Nevertheless, an exact molecular signalling pathway concerning how nicotine induces atrial fibrosis has not yet been described.6

Shan et al. used a canine model to analyse the effect of nicotine on atrial structural remodelling.7 Application of nicotine intravenously at a maximal dose of 50 nmol/L kg⁻¹ for 30 days caused the development of interstitial fibrosis. AF inducibility was increased by up to 15-fold. Interestingly, Shan et al. showed that nicotine causes downregulation of certain atrial microRNA species—miR-133 and miR-590—which was associated with an upregulation of transforming growth factor (TGF)-β1 (the TGF-β1 gene contains putative binding sites for miR-133) and TGF-β receptor type II (the TGF-β receptor gene contains binding sites for miR-590). Levels of connective tissue growth factor (CTGF) increased in parallel with TGF-β1. In contrast to miR-133 and miR-590, levels of several other miRNA species were not affected by nicotine application. Transfection of miR-133 and miR-590 into cultured atrial fibroblasts decreased TGF-β1 and TGF-β receptor type II expression as well as collagen content. These effects were abolished by antisense oligonucleotides against miR-133 or miR-590. Similarly, the application of a 7α nicotine acetylcholine receptor antagonist (α-BTX) also abolished nicotine-induced alterations. In addition to the in vitro results, reduced atrial expression of miR-133 and miR-590 was confirmed in human atrial tissue samples from smokers. Therefore, the study by Shan et al. is the first to show a signalling pathway by which nicotine induces a proarrhythmic atrial fibrosis. The present basic study is of clinical importance due to the high prevalence of AF and its substantial socioeconomic impact. Furthermore, the present paper points towards new therapeutic approaches to prevent atrial structural remodelling by interference with miRNAs, TGF-β1, and CTGF (Figure 1).

MicroRNAs (miRNAs), small RNAs (22 nucleotides long) that were initially described in 1993, regulate key genetic programmes in cardiovascular biology.1,2 They are involved in processes like ventricular hypertrophy, endothelial function, and ventricular arrhythmias post-myocardial infarction. Thus far, 677 human miRNAs have been described. Redundancies among seed sequences could explain that genetic loss of most miRNAs may cause subtle changes in the phenotype only. In mice, depletion of miR-133 is associated with ventricular septal defects and impaired systolic function.9 Overexpression of miR-133 causes thin-walled ventricles and reduced proliferation of cardiomyocytes. In transgenic mice models of left ventricular hypertrophy, overexpression of miR-133 reduces the amount of hypertrophy. In contrast, application of miR-133 antisense oligonucleotides induces the development of left ventricular hypertrophy in wild-type animals.10 Some recent papers link the regulation of miRNAs to the occurrence of cardiac arrhythmias. A study showed that miR-1-overexpressing myocytes exhibited spontaneous arrhythmogenic oscillations of intracellular Ca²⁺ via increased phosphorylation of L-type and RyR2 channels.11 Furthermore, it was demonstrated

* Corresponding author: Tel: +49 391 6713225; fax: +49 391 6713202.
E-mail address: andreas.goette@med.ovgu.de

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that miR-1 is overexpressed in individuals with coronary artery disease, and that when overexpressed in normal or infarcted rat hearts, it exacerbates arrhythmogenesis.\textsuperscript{14} It was further shown that miR-133 repressed KCNQ1, a channel protein responsible for the slow delayed rectifier K\textsuperscript{+} current in cardiac cells, which points to a role of miR-133 in abnormal QT prolongation.\textsuperscript{15}

The elegant study by Shan et al.\textsuperscript{16} extends our knowledge about the impact of nicotine and miRNAs on proarrhythmic atrial remodelling. Besides the described profibrotic effects, however, nicotine inhibits ionic currents in a concentration-dependent manner.\textsuperscript{16} Recent animal experiments have also shown that nicotine base has significant effects on atrial refractoriness and facilitates the inducibility of AF, especially in older animals.\textsuperscript{5} Thus, a limitation of the present study is that direct electrophysiological effects of nicotine are not specifically presented. Nevertheless, Shan et al. show very convincingly that reduced amounts of miR-133 and miR-590 increase atrial fibrosis via TGF-\beta1. Unfortunately, the precise intracellular mechanisms involved in downregulation of miRNA after activation of the nicotine receptor (\alpha7-nAChR) are still unknown, and further studies are necessary to get a more complete picture of the involved signalling cascades. It can be speculated that alterations in miRNA processing from pri-miRNA to pre-miRNA to miRNA might occur. It may be that even in non-smokers, specific regulation of miRNAs contributes to proarhythmic atrial changes. Therefore, the present study will stimulate and expand further research in this highly interesting and innovative field. In addition, interference with miRNAs using small silencing RNAs or antisense oligonucleotides has the potential to be developed as novel therapeutic approach to AF.

References


