Editorial Comment

Making Sense of Antisense Therapy for Hypertension

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Adrenoceptors are intimately involved in the regulation of vascular tone. Whilst pharmacological antagonism of β-adrenoceptors is still part of the mainstay treatment for hypertension, α-adrenoreceptor blockade is rarely used as a front line therapy.[1] In the ALLHAT study peripheral α-blockade in high risk hypertensive patients led to a 25% increase in cardiovascular events and doubled the likelihood of hospital admissions.[2] Although efficacious, centrally acting α_2-receptor antagonists such as clonidine, medetomidine, and methyldopa are used infrequently because of their narrow therapeutic index. Defining the functional role of the three different α_2-receptor subtypes affords the possibility of improving efficacy and reducing side effects.[3]

Pharmacological studies have shown that α_{2A}-adrenoreceptor-blocking drugs act predominantly in the nucleus tractus solitarii by inhibiting sympathetic drive to the heart and vessels, leading to a reduction in blood pressure. It has been reported that α-adrenoreceptor agonist stimulation in mice with targeted deletion of the α_{2B}-receptors results in blood pressure reduction,[4] whilst the same is not true for α_{2A}-receptors made non-functional through a point mutation.[5] Using the technology of genetically modified mice, it has been established that α_{2A}-receptors exert a tonic sympathoinhibitory function centrally and a vasoconstrictive effect peripherally; the α_{2B}-receptors act centrally, causing the hypertensive sympathoexcitatory response to salt, but have no direct effect on vascular wall structures; while the α_{2C}-adrenoreceptor seems to have no haemodynamic function.

In this issue of the journal Triantafyllidi et al[6] report that modulation of α_{2B}-receptor gene expression in the spontaneously hypertensive rat results in hypotensive episodes of short duration. The author uses a cytomegalovirus promoter-driven antisense against α_{2B}-receptor mRNA delivered intraventricularly via a plasmid vector. Previously, it has been shown using similar strategies that α_{2B}-receptors are involved in the maintenance of hypertension in a model of salt-induced hypertension.[7,8] The current work adds to this understanding by using a less specific model in the spontaneously hypertensive rat. Indeed, blood pressure is regulated through multiple overlapping pathways, and the current study points towards this with a short lived benefit of 1 day compared with 8 days in the salt-induced hypertension model. Furthermore, using fluorescence imaging the author identifies the primary area of uptake of antisense DNA as the nucleus tractus solitarii, a site of termination of cardiac sympathetic afferents.

The expression and synthesis of cellular proteins is a coordinated process involving multiple steps. Antisense therapy works by inhibiting DNA uncoiling, transcription or splicing and RNA export, stability or translation, ultimately blocking gene expression.[9]

Successful antisense therapy requires the agent be stable *in vivo*, capable of binding to the target with high affinity, and specific to suppression of the particular gene. Chao and colleagues were among the first to demonstrate that sense approaches could reduce blood pressure via delivery of genes to kallikrein and atrial natriuretic peptide.[10,11] As novel highly efficient vectors become available, their use as delivery vehicles for the treatment and control of hypertension will grow. This will only be possible if further studies such as Triantafyllidi's continue to attempt to show reproducibility of the benefits of antisense therapy in different models of the same disease.

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