Development and usefulness of transgenic rabbit models of inborn arrhythmogenic diseases

Appendices

Valorisation Addendum

Inborn genetic defects causing prolongation or shortening of the QT interval are rare, but they affect young people with a potentially long lifespan. As the heart relies on a delicate balance of ion currents to maintain the rhythm, and subtle, but important differences in these currents exist between different parts of the heart (as well as differences in counter-regulation), neither single cell experiments nor computer simulation of the heart are sufficiently accurate.

Therefore, animal models are indispensable to analyse the mechanisms of arrhythmia generation in heritable arrhythmogenic diseases. As the commonly used mice have markedly different electrophysiological and biochemical properties of the heart, their usefulness for translational research beyond proof-of-concept studies is very limited. This is opposed to rabbits, which show marked similarity of their hearts regarding depolarizing and repolarizing currents and their respective ion channels. The here presented transgenic animal models of Long- (LQTS1 and LQTS2) and Short (SQTS) QT-Syndromes are the first to mimic the human phenotype from the cellular, organ to in vivo level in nearly all aspects.

This enabled for the first time to study not only the mechanism of arrhythmogenesis, but also the influence of various factors, such as age, sex-hormones (oestrogen, gestagen, testosterone) and hormones of post-partum and lactation (oxytocin and prolactin). Similarly, the models are useful to test new treatment strategies aimed to normalize the altered repolarization form the cellular, the whole organ to the in vivo level. Pharmacological interventions using drugs such as Nicorandil, NS1643, or nutrients such as decosahexaenic-acid have already been tested, currently genetic interventions in vivo using suppression-and-replacement constructs (see chapter 9.5) are on the way.

Overall, the results of the studies presented here enabled and continue to enable important steps in our understanding of QT related diseases and the development of targeted (gene specific) therapies.