O6-5

Clinical application of a vagal hyperreactive animal model.

Helms P.(1), Livolsi A.(1,2), Niederhoffer N.(1), Dali-Youcef N.(4,5), Rambaud C.(7), Olexa C.(1,2), Mokni W.(1), Gies J.P.(3), Bousquet P(1,6)
1 Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Strasbourg, France, 2 Pole Pediatrique Medico-Chirurgical,
Hopitaux Universitaires, Strasbourg, France, 3 Laboratoire de Biophotonique et de Pharmacologie, Strasbourg, France, 4 Institut de Genetique et de Biologie Moleculaire et Cellulaire, Strasbourg, France, 5 Laboratoire de Biochimie Generale et Specialisee, Hopitaux Universitaires, Strasbourg, France, 6 Centre d'Investigation Clinique, Hopitaux Universitaires-INSERM, Strasbourg, France; 7 Service d'Anatomie Pathologique et Medecine legale, Garches, France

Vagal hyperreactivity is known as a cause of vasovagal syncopes, and has been proposed as a possible cause of sudden infant death syndrome (SIDS).
In a first study, rabbits with marked vagal pauses following injection of phenylephrine were selected and crossed to obtain a vagal hyperreactive (VHR) strain. In binding experiments, we observed an overexpression of M2 and M3 muscarinic receptors density in the heart of this VHR rabbit model (Bmax (fmolmg-1prot) M2 : 148,7 ± 72,6 vs 65,6 ± 18,9, $p<0.05$; Bmax M3: 226,9 ± 77,3 vs 88,6 ± 30,1, $p<0.05$); the severity of the phenylephrine induced bradycardia was correlated with the density of the muscarinic receptors. In addition, those rabbits displayed an acetylcholine esterase (AchE) mRNA amplification ratio of 3.6 in heart cells versus normal rabbits. Seeking blood markers, we found that M2 mRNA expression level in lymphocytes was about 10 times higher in our VHR model compared to that observed in normal rabbits, and that it was associated with twice the AchE enzyme activity in erythrocytes.
In a second study, we aimed to seek biological abnormalities in the peripheral vago-cardiac system in SIDS victims. Left ventricular samples were obtained from autopsies of SIDS (n=9) and children deceased from non cardiac causes (n=11). Binding experiments performed with a selective muscarinic ligand showed that the muscarinic receptor density in the heart of SIDS victims was more than double that found in samples from children who died from other causes.
In conclusion, we showed that overexpression of cardiac muscarinic receptors may play a critical role in a VHR animal model and in infants deceased from SIDS. Furthermore, a same pattern of changes was detected in peripheral mononuclear white blood cells in rabbits. Muscarinic receptor expression level in peripheral mononuclear white blood cells could become a reliable and easily measurable marker of risk of vasovagal syncopes and sudden death which could be of great clinical interest.