INFLUENCE OF β_1-ADRENOCEPTOR POLYMORPHISMS ON THE EXPRESSION OF β_1-ADRENOCEPTORS IN HUMAN LUNG TISSUE

L.J. Kay[1], S.K. Suvarna[2], R. Chess-Williams[3] and P.T. Peachell[1]. [1]Academic Unit of Clinical Pharmacology, University of Sheffield. [2]Histopathology, Northern General Hospital, Sheffield. [3]Faculty of Health Sciences and Medicine, Bond University, Queensland, Australia.

Human lung tissue contains both β_2- and β_1-adrenoceptors at a reported ratio of 4:1 (Sano *et al.,* 1993). However, previous work within our group has shown extensive variability in the expression of β-adrenoceptors in human lung. The possibility that genetic polymorphisms in β-adrenoceptor genes might influence receptor expression has been explored. A statistically significant ($P<0.05$) association between a single nucleotide polymorphism (SNP) in the β_2-adrenoceptor gene (491 C>T) and β_2-adrenoceptor expression has been observed in human lung tissue (data unpublished). The aim of the present study was to determine whether a similar association might exist between two common SNPs (145 A>G (Ser49Gly) and 1165 C>G (Arg389Gly)) in the β_1-adrenoceptor gene and β_1-adrenoceptor expression.

Human lung tissue (n=78) was obtained from surgical resections. Saturation binding assays using ^{125}I-iodocyanopindolol (0.0156 - 2 nM) were performed on membrane fractions of lung tissue and specific binding assessed using methods that have been described (Nishikawa *et al.,* 1996). Discrimination of β_2- and β_1-adrenoceptors was determined using the selective β_1-adrenoceptor antagonist, CGP20712A (0.01 μM). For genotypic analysis, genomic DNA was extracted from a small amount of human lung tissue, and genotype determined by PCR-RFLP using the restriction enzymes *Eco*0109I (145 A>G) or *Bsm*FI (1165 C>G). Data were analysed using GraphPad Prism software. Statistical significance was determined using either Mann-Whitney or Kruskal-Wallis tests.

In human lung tissue (n=78), β_1-adrenoceptor densities ranged from 0 to 46 fmol mg^{-1} protein (mean±s.e.m; 8±1 fmol mg^{-1} protein). All 78 preparations were genotyped at positions 145 and 1165 of the β_1-adrenoceptor gene. Both SNPs where shown to be in Hardy-Weinberg equilibrium, as evaluated by χ^2 goodness of-fit-tests. Since only 2 preparations were found to express the less common allele at position 145, these data were not included in the statistical analysis. Neither position 145 A>G, nor 1165 C>G appeared to influence β_1-adrenoceptor density ($P>0.05$; see table 1).

Table 1

	Nucleotide position					
	145			*1165*		
	A	*A/G*	*G*	*C*	*C/G*	*G*
n	63	13	2	41	33	4
β_1-adrenoceptor density (fmol mg^{-1} protein)	8±1	10±3	1 & 3	8±1	8±2	5±3

To conclude, preliminary findings suggest that, although there is extensive inter-individual variability in β_1-adrenoceptor densities in lung, this is not influenced by SNPs 145 A>G or 1165 C>G of the β_1-adrenoceptor gene.

Nishikawa, *et al.,* (1996). *Eur J Pharmacol*, **318**,123-129
Sano, *et al.,* (1993). *Life Sciences*, **52**, 1063-70