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COMMENTARY

The α_{1L}-adrenoceptor is an alternative phenotype of the α_{1A}-adrenoceptor

CP Nelson

Department of Cell Physiology and Pharmacology, University of Leicester, Henry Wellcome Building, Leicester, UK

Despite over two decades of research, the molecular identity of the α_{1L}-adrenoceptor phenotype has remained elusive. In this issue of the *BJP*, Gray *et al*. (2008) provide persuasive evidence that the *in vivo* α_{1L}-adrenoceptor phenotype requires the expression of the α_{1A}-adrenoceptor gene. They have shown that in mice lacking the functional α_{1A}-adrenoceptor gene, α_{1L}-mediated responses to noradrenaline in prostate smooth muscle are substantially attenuated. These findings support earlier evidence that the α_{1L}-adrenoceptor profile represents a functional phenotype of the α_{1A}-adrenoceptor gene product, but additional cell background-dependent factors must act in concert with the α_{1A}-adrenoceptor protein to determine whether an α_{1L}- or a classical α_{1A}-adrenoceptor profile is expressed. The challenge remains to establish the nature of these cellular factors and the mechanism(s) by which they influence G-protein-coupled receptor pharmacology.
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Abbreviations: BPH, benign prostatic hyperplasia; GPCR, G-protein-coupled receptor

In the 'post-genomic' era, much attention has been focused on the study of the physiological roles and endogenous ligands for previously undiscovered G-protein-coupled receptors (GPCRs), identified from genomic sequencing (so-called 'deorphanization'). In contrast, the α_1-adrenoceptor field has struggled with the opposite conundrum—a pharmacologically defined receptor phenotype, which has resisted molecular definition. Genes have been identified for three isoforms of the α_1-adrenoceptor (termed α_{1A}, α_{1B} and α_{1D}), but the fourth α_1-adrenoceptor phenotype, α_{1L}-adrenoceptor, has until now been defined purely on the basis of a characteristically low affinity for a number of selective antagonists, including prazosin (Guimaraes and Moura, 2001). However, this phenotype is of physiological significance, as the α_{1L}-adrenoceptor profile has been identified in a variety of tissues, across a number of different species (see Guimaraes and Moura, 2001), where it regulates smooth muscle contractility in the vasculature and the lower urinary tract. It may also be of clinical relevance, as α_1-adrenoceptor antagonists such as tamsulosin are a front-line therapy for benign prostatic hyperplasia, where they effectively and selectively relax prostatic smooth muscle, providing symptomatic relief for BPH patients (Milani and Djavan, 2005).

Correspondence: Dr CP Nelson, Department of Cell Physiology and Pharmacology, University of Leicester, Henry Wellcome Building, Lancaster Road, Leicester, LE1 9HN, UK.
E-mail: cpn5@le.ac.uk
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It has previously been proposed that the α_{1L} phenotype may represent an alternative conformational state of the α_{1A}-adrenoceptor gene product (Ford *et al*., 1997). When recombinantly expressed in Chinese hamster ovary cells, the α_{1A}-adrenoceptor exhibited a classical α_{1A}-adrenoceptor profile in radioligand-binding assays in membrane homogenates, but in [^{3}H]-inositol phosphate accumulation assays in intact cells, a number of antagonists (including prazosin and 5-methylurapidil) displayed lower affinities, consistent with the pharmacological profile of the α_{1L}-adrenoceptor (Ford *et al*., 1997). In addition, whereas the native α_1-adrenoceptor expressed in rat prostate smooth muscle exhibited an α_{1A} profile in membrane radioligand-binding assays, the functional (contractile) phenotype in the same tissue was that of an α_{1L}-adrenoceptor (Hiraoka *et al*., 1999). These (and other) early studies, therefore, pointed to the α_{1L}-adrenoceptor being the functional manifestation of the α_{1A}-adrenoceptor gene product. However, the dependence upon assay conditions (that is, functional assays in intact cells/tissues versus radioligand-binding assays in membrane homogenates) of the observed phenotype, allied to the fact that functional α_{1A} profiles can be observed in some tissues (see Guimaraes and Moura, 2001 and references therein) has confounded attempts to establish the relationship between the α_{1A}- and α_{1L}-adrenoceptors.

An analogous situation to the atypical pharmacological profile of the α_{1L}-adrenoceptor is that of the putative β_4-adrenoceptor, a phenotype defined by resistance to classical β-adrenoceptor antagonists and activation by so-called 'non-conventional partial agonists' (Kaumann,

1989). The molecular identity of this phenotype (as a novel 'state' of the β_1-adrenoceptor) was identified by the use of 'knockout' mice lacking combinations of β-adrenoceptors (see Granneman, 2001 and references therein). In this issue of the *BJP*, Gray *et al*. (2008) apply a similar approach to provide the first definitive evidence that the manifestation of the α_{1L}-adrenoceptor phenotype (at least, in mouse prostate smooth muscle) is dependent upon the expression of the α_{1A}-adrenoceptor gene product. Using a range of antagonists known to display selectivity between the α_{1A}- and α_{1L}-adrenoceptor profiles, the authors have previously characterized the noradrenaline-mediated contraction of mouse prostate smooth muscle as being mediated by an α_{1L}-adrenoceptor (Gray and Ventura, 2006). In the present study, Gray *et al.* (2008) utilized 'knockout' mice lacking a functional α_{1A}-adrenoceptor gene (Rokosh and Simpson, 2002), to investigate the role of this gene in the observed α_{1L} *in vivo* phenotype. They found that responses to noradrenaline were attenuated by approximately 80% in prostates from mice homozygous for the disrupted α_{1A}-adrenoceptor gene, compared with wild-type mice, providing strong evidence that the expression of the α_{1L}-adrenoceptor in mouse prostate smooth muscle requires the presence of a functional α_{1A}-adrenoceptor gene (Gray *et al.*, 2008).

In addition, the authors also examined contractile responses to electrical field stimulation, an experimental paradigm more closely resembling physiological stimulation. This contraction was partially inhibited by prazosin and the contraction to high-frequency stimulation was approximately 30% smaller in mice lacking the functional α_{1A}-adrenoceptor than in wild-type mice (Gray *et al.*, 2008). Importantly, the residual contraction (most probably mediated by non-adrenergic, non-cholinergic transmitters) was insensitive to prazosin, indicating that all of the $\alpha_{1A/L}$-adrenoceptor-mediated contraction was lost in the absence of the α_{1A} gene. The case might have been strengthened if the authors had demonstrated that the adrenergic component of the electrical field-stimulated contraction was mediated by α_{1L}-adrenoceptors, as the authors themselves acknowledge that the receptors mediating responses to nerve stimulation could differ from those mediating the response to exogenous noradrenaline. However, together with their findings with exogenously applied noradrenaline, these data provide the strongest evidence thus far that the α_{1A}-adrenoceptor gene is essential for the generation of the α_{1L}-adrenoceptor phenotype.

Providing that the dependence of the α_{1L} phenotype upon α_{1A}-adrenoceptor gene expression is universally applicable (across all species/tissues where the α_{1L} phenotype has been identified), the next question to address is what determines whether an α_{1A}-adrenoceptor exhibits an α_{1L}- or a classical α_{1A}-adrenoceptor phenotype? The fact that functional responses in certain tissues display a classical α_{1A}-adrenoceptor profile (see Guimaraes and Moura, 2001) suggests that the α_{1L}-phenotype is not simply the default functional profile of the α_{1A}-adrenoceptor gene product, raising the possibility that tissue-dependent cellular factors may govern the observed phenotype (Nelson and Challiss, 2007). It is well established that the cellular environment can influence GPCR signalling and agonist pharmacology, but the traditional view that the antagonist pharmacology is independent on the cellular context may also need to be reevaluated (Nelson and Challiss, 2007).

Evidence has recently been presented that the intact cellular environment is important for the manifestation of the *in vivo* α_{1L}-adrenoceptor phenotype (Morishima *et al.*, 2007, 2008). These studies have shown that both α_{1A}- and α_{1L}-adrenoceptor populations can be distinguished in radioligand-binding assays in intact tissue segments, but that upon tissue homogenization and membrane preparation, the α_{1L}-adrenoceptors are either degraded or converted to α_{1A}-adrenoceptors (Morishima *et al.*, 2007, 2008). Clarification of what is happening to the α_{1L}-adrenoceptor population upon its isolation in membrane homogenates might provide valuable clues as to the cellular factor(s) responsible for shaping the pharmacological profile of the α_{1A}-adrenoceptor gene product. Numerous mechanisms for generating phenotypic pharmacological profiles of GPCRs have been identified (see Nelson and Challiss, 2007 and references therein) and as our appreciation of the complexity of GPCR signalling advances, so does the list of possibilities. The identification of the α_{1L}-adrenoceptor as an alternative phenotype of the α_{1A}-adrenoceptor represents a significant advance in our understanding of this phenomenon and will hopefully provide a springboard for future progress in elucidating the mechanisms underlying these distinct phenotypes.

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