

COMMENTARY

α_1-Adrenoceptor subtype substitution in knockout mice

*,[1]J Paul Hieble

[1]Department of Urology Research, GlaxoSmithKline, King of Prussia, PA, U.S.A.

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Since the discovery of α_1-adrenoceptor subtypes, there has been continued interest in the identification of their functional roles. This has been facilitated by the availability of increasingly selective antagonists for individual subtypes, especially for the α_{1A} and α_{1D}, as well as knockout (KO) mice lacking either α_{1A}, α_{1B} or α_{1D} adrenoceptors (Hague *et al*., 2003).

In some tissues, such as heart or blood vessels, multiple α_1 subtypes are present and produce the same functional response, although the dominant subtype can vary between species or particular blood vessels (Hrometz *et al*., 1999). In other cases, such as in most urogenital smooth muscles, the response is mediated primarily by a single subtype (α_{1A}) independent of species (Ruffolo & Hieble, 1999). Depending on the species, the dominant α_1-adrenoceptor mediating metabolic responses in the liver is either α_{1A} (human, cat, dog, rabbit) or α_{1B} (rat, mouse, hamster). In the monkey, hepatic α_{1A} and α_{1B} adrenoceptors both contribute (Garcia-Sainz *et al*., 1996). In this issue of British Journal of Pharmacology, Deighan *et al*. (2004) show that, in α_{1B} KO mice, the function of the hepatic α_{1B} adrenoceptor can be assumed by the α_{1A}.

Radioligand-binding assays show RS100329, a selective α_{1A} antagonist, to have 30-fold greater affinity for α_1-adrenoceptors in hepatocytes from the KO animals ($pK_i = 9.3$) than in WT animals ($pK_i = 7.8$). In contrast, the selective α_{1D} antagonist BMY 7378 had low affinity in both WT and KO mice ($pK_i = 6.3$ and 6.2, respectively).

At 4 months of age, the liver from α_{1B} KO mice had a substantial α_1-receptor binding (30 fmol mg^{-1} protein), although less than WT mice of the same age (50 fmol mg^{-1} protein). However, 3-month-old KO mice had almost no hepatic α_1-adrenoceptor binding. This would indicate that replacement of the missing α_{1B} adrenoceptor by the α_{1A} is a relatively slow process, and suggest that, in general, comparisons of receptor density between WT and KO mice should be made at multiple time points.

Based on multiple literature reports, it is now clear that α_1-adrenoceptors are not confined to the cell membrane, and that the subcellular localization can differ between subtypes (Mackenzie *et al*., 2000; Stanasila *et al*., 2003; Hague *et al*., 2004). Deighan *et al*. (2004) show that the distribution of α_{1A} adrenoceptors in KO mice is identical to that of the α_{1B} in WT mice, consistent with the ability of the two subtypes to mediate the same physiological function.

This report raises several interesting questions for future research. For example, what adrenoceptor subtype mediates hepatic function in the α_{1A}/α_{1B} double KO mouse (O'Connell *et al*., 2003), which has no obvious metabolic defects? Can one of the other α_1 subtypes mediate aortic vasoconstriction in α_{1D} KO mice?

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*Author for correspondence; E-mail: j_paul_hieble@gsk.com
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