6. Agonist-Induced Down-Regulation of $\beta_1$-Adrenergic Receptors: Possible Biochemical Rationale for Novel Antidepressants

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Changes in the linkage between the serotonergic and noradrenergic neuronal systems at the level of the norepinephrine (NE) receptor coupled adenylate cyclase is currently the favored hypothesis to explain the mechanism of action of antidepressant drugs. In particular, the down-regulation of $\beta$-adrenoceptors (BARs), which is associated with a subsensitivity of the receptor-coupled adenylate cyclase, has been postulated as a marker of antidepressant efficacy as the time course for this action corresponds closely with the onset of clinical therapeutic effects. It has also been proposed that centrally acting BAR agonists, which interact directly with the receptor, could down-regulate BARs in the brain more quickly than classical antidepressants and would therefore cause rapid-onset antidepressant effects in patients.

In order to explore this hypothesis, investigators have attempted to demonstrate rapid-onset down-regulation of central nervous system $\beta$-receptors by BAR agonists and a rapid-onset antidepressant effect in patients. In fact, long-term exposure to BAR agonists does lead to an attenuation of tissue responsiveness to $\beta$-adrenergic stimulation due to decreased receptor density and/or diminished adenylate cyclase activity. In particular, clenbuterol and salbutamol are claimed to possess fast-acting antidepressant properties.

In our laboratory we have been interested not only in the time course of BAR regulation but also in determining which, if either, of the BAR subtypes is preferentially down-regulated by classical antidepressants and by potential fast-acting "BAR agonists type antidepressants."

In this study in rats, the effects of chronic dosing with the BAR agonists clenbuterol and prenalterol were compared with those of the tricyclic desipramine. The drugs or vehicle were administered subcutaneously to male Sprague-Dawley rats at a rate of 20 mg/kg/day using osmotic Alzet pumps. The pumps were removed after 8 days, and the rats were killed 24 h later. The total BAR population was determined, in cerebral cortex, by saturation analysis on crude synaptosomal membrane preparations. The chosen radioligand was (−)$^{[125]}$I$pindolol$ ($20$−$800$pm) and (−)$\text{iso}-prenaline$ ($200 \mu M$) was used to define nonspecific binding. The addition of the highly selective $\beta_1$-adrenoceptor antagonist $\text{CGP 20712A (100 nM)}$ to the assay medium converted the heterogeneous populations of BAR populations to
essentially homogeneous $\beta_2$-adrenoceptor populations. They were then available for measurement with ($-$)[125I]pindolol. The remaining $\beta_1$-adrenoceptor population was then estimated by subtraction.

Using these techniques we have been able to confirm that desipramine is a selective down-regulator of $\beta_2$-adrenoceptors, by 40% in cerebral cortex (Fig. 6.1; Table 6.1). This finding was previously suggested by Minneman et al., who employed the $\beta_2$-adrenoceptor selective agonist zinterol in displacement-type binding studies; by Dooley et al., who used various tissue types; and by Kitada et al., who conducted behavioral studies. Hence any potential fast-acting $\beta$AR agonist

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure6.1.png}
\caption{Effects of 8 days of treatment with vehicle ($n = 9$), desipramine ($n = 7$), clenbuterol ($n = 7$), or prenalterol ($n = 6$) on the maximal binding capacity of ($-$)[125I]pindolol to total $\beta_2$-adrenoceptors, and $\beta_2$-adrenoceptors in rat cerebral cortex. Each column represents the mean value, and the vertical lines show SEMs. Significantly different from control: **$p < 0.01$; *$p \leq 0.05$.}\
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