Intrinsic Sympathomimetic Activity of β-Adrenoceptor Blocking Agents

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Summary. The pharmacological methods used to assess the intrinsic sympathomimetic activity (ISA) of β-blockers are discussed. The clinical relevance of ISA to respiratory function, peripheral resistance and cardiac function is reviewed. It appears doubtful whether ISA is always of predominant clinical significance and an alternative explanation is offered for many clinical effects observed with certain β-blockers, e.g. pindolol, oxprenolol, tolamolol, metoprolol, etc. Some effects of these β-blockers resemble those of labetalol, a new drug with both α- and β-blocking activity. Some clinical effects of certain β-blockers are more likely to be due to α-blocking activity than to their ISA.

Key words: β-Blockers, α-blocking, activity, intrinsic sympathomimetic activity, partial agonist.

β-adrenoceptor blocking drugs (β-blockers) were introduced into clinical use in 1962 [12], almost fifteen years ago. Many reviews have summarized their pharmacology and their multiple clinical applications [3, 7, 19, 20, 23, 27, 39, 47, 60, 62]. By definition, β-blocking agents are substances that have an affinity for β-adrenergic receptors, but have no independent pharmacological action themselves [5]. In other words, their interaction with the receptors does not result in an effect or response, but the receptors cannot respond to agonists, since they are occupied by the β-blocking molecules. It is usually accepted that many β-blockers cause a measurable agonist response when interacting with β-receptors [5, 26]. This is interpreted as evidence for partial agonist activity of these substances, often defined as Intrinsic Sympathomimetic Activity (ISA). The maximum response which can be obtained is less than that of isoprenaline or adrenaline, although the affinity of the β-blocking agent for the β-receptor site is high [5]. Of course the activity of β-antagonists is greater than the ISA, otherwise these drugs would not be used to antagonize the effects of catecholamines on the β-receptors. We consider that the clinical relevance of the ISA of β-blockers can be questioned.

Pharmacological Evidence for Intrinsic Sympathomimetic Activity

Pharmacologists can assess the ISA of β-blockers only by using complicated methods, most commonly involving in vitro preparations. Sometimes use is made of animals pretreated with catecholamine-depleting drugs in high dose, such as reserpine or syringoserpine, and the animal are anaesthetized and often pithed to increase their sensitivity to catecholamines [1, 8, 46]. Under these circumstances, if a certain increase in heart rate is observed, it is concluded that the β-blocker has ISA. This thesis is further confirmed if propranolol, which has no ISA, counteracts the increase in heart rate. The number of technical intricacies involved in determining small increases in heart rate should alert one to the possibility that the data produced by such methods may represent artefacts. For the in vitro tests it is essential to keep a stable pH, ionic environment and temperature. Anaesthesia, pithing, artificial ventilation and premedication are necessary in animal experiments. Under such conditions the complexity and difficulty of detection of the possible role of α-receptors and artefacts defy the possibility of objective analysis [57].

Relevance of Intrinsic Sympathomimetic Activity

By using a β-blocker with ISA, there should be less risk of precipitating respiratory failure or of increas-
ing arteriolar resistance, i.e. a high degree of cardioselectivity, less bradycardia and less cardiodepressive effect than with a β-blocker without ISA [26]. It is a fact that some β-blockers with ISA, e.g. pindolol, induce less bradycardia and bronchospasm than propranolol. However, it is not certain that these effects depend on the ISA. Waal-Manning and Simpson, having observed a certain increase in blood pressure with a relatively high dose of pindolol, have explained this “paradoxical hypertension” by the powerful ISA of this β-blocker [61]. However, on reading their report, it will be seen that there were no signs of β-receptor stimulation and that, in particular, tachycardia was absent. Moreover, a powerful β-agonist effect of pindolol should have induced arteriolar vasodilation, as in the case of isoprenaline infusion, and so decreased arteriolar resistance, and it would probably also have produced hypotension rather than hypertension. Further supporting evidence against the relevance of ISA in the above case comes from reports that a rise in blood pressure has been also observed with propranolol [13, 25], acebutolol, practolol and sotalol [28]. Other explanations should be sought. Recent studies have demonstrated that a certain increase in blood pressure can be observed in a minority of hypertensive patients treated with propranolol, and that this may depend on the increase in arteriolar resistance caused by blocking of vascular β-receptors and unopposed activity of catecholamines on the α-receptors [13, 25]. Furthermore, particularly in patients with low-renin activity in plasma, treatment with propranolol may induce fluid retention [25]. Other authors have observed that pindolol, like other β-blockers, not only decreases blood pressure but also has a variable effect on plasma-renin activity, which may also be increased [17, 18, 40, 53, 54, 55]. Again, the increase in plasma-renin activity has been attributed to the powerful ISA of pindolol [53, 54]. However, other possibilities can be considered. It has been observed that acute administration of pindolol may have a negative effect on renal function in the rat [48] and in man [31], and there is no reason to consider that these effects on renal function depend on ISA of pindolol or are secondary to renin stimulation. Pindolol and metoprolol, both with ISA, may stimulate noradrenaline secretion [45]. Given orally, propranolol produces a active metabolite, 4-hydroxypropranolol, which has ISA. Nevertheless, the effects of oral propranolol can easily be distinguished from those of pindolol or oxprenolol, for example. It is conceivable that the differences may not depend on ISA alone and that other factors should also be considered.

α-Adrenoceptor Blocking Activity

In theory, a β-blocker should not interfere with α-receptors, at least not directly. In 1966, Govier and associates demonstrated that even isoprenaline possesses some minor α-agonistic actions [29], and others have confirmed their experience [23, 57, 59]. Kunos and Szentivanyi have shown that by changing the temperature of in vitro preparations of frog and cat hearts, the affinities of α- and β-agonists and antagonists can be completely changed: at higher temperatures the effects of adrenaline and noradrenaline could be antagonized by β-blocking agents, whereas at lower temperatures the effects of these catecholamines were antagonized by α-blocking drugs [36]. Kunos and coworkers also demonstrated that the arteries of rats with hypothyroidism (produced by thyroidectomy) were less sensitive to β-agonists, whereas their sensitivity to α-agonists was increased [37]. The reverse was true for rats with hyperthyroidism [37]. Hagino has confirmed these results [30]. These experiments show that the sensitivity of α- and β-adrenoceptors is, at least in part, hormone dependent.

Conclusions: Variability of Receptors

A drug is now available, labetalol, which antagonizes the effects of catecholamines on both α- and β-receptors [15, 41]. Tolamol, pindolol and oxprenolol, β-blockers with ISA, should also possess some α-blocking activity [6, 20, 45, 56]. Interestingly, the effect of labetalol on plasma-renin, namely an increase in renin despite a good hypotensive effect, is qualitatively and quantitatively similar to that of pindolol [17]. This effect of labetalol on renin secretion may also be due to the marked hypotensive action of the drug, i.e. an indirect effect, and not due to the α-blocking activity of the compound. Labetalol does not produce significant effects on respiratory function, since its effects on the β- and α-receptors buffer each other [52]. However, similar clinical behavior is observed with acebutolol, atenolol, metoprolol, tolamol, pindolol and, to a lesser extent, oxprenolol (the α-blocking activity of which should be minimal) [1, 2, 4, 9, 10, 11, 14, 35, 50, 51]. Some of these β-blockers are relatively unselective. Is it possible that their effect is, at least in part, the consequence of their α-blocking activity, as is the case with labetalol?

Administered acutely, pindolol does not increase peripheral resistance, and it may even decrease this parameter [6, 43]. Under the same conditions, pro-