Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst116P.pdf

Comparison Of The Agonist Activities Of Treprostinil And Naxaprostene In Rat Tail And Pulmonary Arteries

Treprostinil is used to treat pulmonary hypertension, however its mechanism of action may involve more than prostacyclin (IP) receptors, as Whittle et al (2012) have shown that it activates human recombinant prostanoid DP1, EP2 and IP receptors. In view of the recent emergence of highly selective EP2 receptor antagonists (af Forselles et al., 2011), it was aimed to investigate whether the current prostanoid antagonists were adequate to unfold a rather complex pharmacology of treprostinil. Treprostinil lacks the ether oxygen moiety at C6-9 present in prostacyclin (PGI2) and has a benzene ring inserted in its α-chain. Naxaprostene also has both functionalities, so we compared its inhibitory profile with that of treprostinil. 5 mm rings of rat tail (rTA) and pulmonary (rPA) arteries were mounted under isometric conditions (resting tension of 0.75-1.0 g) in 10 ml baths at 37°C. Contractions were elicited by phenylephrine (300-600 nM). We used BW-245C (10-100 nM), ONO-AE1-259 (3-30 nM), TCS-2510 (1-10 nM) and AFP-07 (0.3-30 nM) as selective DP1, EP2, EP4 and IP agonists respectively. The corresponding antagonists were BW-A868C and MK-0524, ACA-23, GW-627368 and RO-1138452 (Jones et al., 2009). A simple antagonist reversal protocol showed that rTA contains inhibitory EP4 and IP receptors, while rPA predominantly exhibited IP receptors. In further experiments, rTA was pretreated with 3 of the antagonists (BW-A868C / ACA-23 / GW-627368), followed by cumulative doses of treprostinil or naxaprostene and finally followed by the fourth antagonist (CAY-10441) in an attempt to reverse relaxation. In this way we could apportion EP4 and IP agonism to treprostinil, but only IP agonism to naxaprostene which behaved as a partial agonist. The relevance of these findings to the therapeutic use of prostacyclin analogues will be discussed. af Forselles KJ *et al*. (2011). *Br J Pharmacol* **164**: 1847-1856. Jones RL *et al*. (2009). *Br J Pharmacol* **158**: 104-145. Whittle BJ *et al*. (2012). *Biochem Pharmacol* **84**: 68-75.