The role of the K2P channels TASK-1, TREK-1 and TREK-2 in the use of treprostinil therapy in pulmonary arterial hypertension

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Introduction: Pulmonary arterial hypertension (PAH) is a progressive and ultimately fatal disease affecting ~6 people per million, per year (1). Recent studies have reported mutations in the two-pore domain potassium (K2P) channel TASK-1 (KCNK3) giving rise to PAH (2). Treprostinil is a stable prostacyclin analogue often administered as a therapy in PAH, to keep blood vessels open. It's mode of action is thought to occur through an interaction with prostanoid receptors, DP_2 EP_2 and IP (3). Patients undergoing continuous subcutaneous treprostinil infusion can often exhibit severe pain at the site of delivery (4). In this study we investigate the action of treprostinil on TASK-1 and on two other K2P channels, TREK-1 (KCNK2) and TREK-2 (KCNK10), which regulate the excitability of sensory neurons and are implicated in pain (5).

Method: Using the whole-cell patch-clamp technique, currents were measured through human TASK-1, TREK-1 and TREK-2 channels transiently expressed in tsA201 cells. TASK-1 was also co-expressed with prostanoid receptors (IP, DP_2 and EP_2). Data are expressed as mean ± SEM (n = cells) of current measured at -40 mV and mean % change ± SEM (n = cells), with statistical analysis performed using a paired t-test.

Results: Acute application of treprostinil (1 µM) on cells expressing TASK-1 channels had no effect on current (control: 234 ± 80 pA; treprostinil: 240 ± 53 pA (n = 5); $p > 0.05$). Co-expression of TASK-1 with various prostanoid receptors, followed by acute application of treprostinil (1 µM) resulted in varying effects on TASK-1 current. In cells expressing WT TASK-1 and IP receptors, the average TASK-1 current significantly decreased by 50% in the presence of treprostinil (control: 333 ± 82 pA; treprostinil (1 µM): 173 ± 46 pA, n = 6, $p < 0.05$). Whilst co-expression of TASK-1 with EP_2 receptors saw a 30% increase in TASK-1 current (control: 294 ± 65 pA; treprostinil (1 µM): 368 ± 78 pA, n = 8, $p<0.05$). Co-expression of TASK-1 with DP_2 receptors saw no significant change (3%) in TASK-1 current (control: 387 ± 45 pA; treprostinil (1 µM): 398 ± 54 pA, n = 5, $p > 0.05$). Interestingly, treprostinil had a potent inhibitory effect on the TREK channels in the absence of prostanoid receptors: TREK-1 WT (80 ± 8%, n = 5; $p<0.05$) and TREK-2 WT (59 ± 9%, n = 5; $p < 0.05$).

Conclusion: In this study, acutely applied treprostinil does not appear to have a direct action on the TASK-1 channel itself, instead its effects appear to occur through the activation of prostanoid receptors and their associated signalling pathways. Conversely, treprostinil demonstrates a direct inhibitory effect on TREK-1 and TREK-2 channels. This effect of treprostinil may explain infusion site pain, a common side-effect of patients on subcutaneous treatment (4). Acute enhancement of these channels at the infusion site could therefore help to reduce discomfort in PAH patients.

References

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