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Oral presentation

Oxidised sGC: a novel therapeutic target in the vasculature

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Background

The heme-containing nitric oxide (NO) receptor, sGC can exist in the NO-sensitive reduced (Fe^{2+}) state and NO-insensitive oxidized (Fe^{3+})/heme free form. Indeed, the redox state of sGC can be probed using the NO-independent sGC activator, BAY 58–2667, which preferentially targets sGC in its oxidized states. We hypothesised that in the resistance vasculature, sGC exists in the Fe^{2+}, Fe^{3+} and heme-free forms and the ratio of these redox states is altered under conditions of oxidative stress.

Materials and methods

Small mesenteric arteries (~300 μm diam) from male Sprague Dawley rats were mounted in small vessel myographs and isometric force measured. Vessels were pre-contracted (~50%) with U46619 and cumulative concentration-response curves to sGC activators which target sGC in its Fe^{2+} (DEA/NO), Fe^{3+} (BAY 58–2667) and heme-free states (BAY 58–2667, PPIX) were examined.

Results

BAY 58–2667 was the most potent vasodilator studied (pEC_{50} = 12.82 ± 0.13, -log M) with a maximal relaxation of 91.9 ± 1.9% (n = 6). Its potency was increased up to 200-fold ($P < 0.0001$) upon oxidation of sGC by ODQ (10 μM, n = 6) and in the presence of the NO synthase inhibitor, L-NAME (100 μM, n = 4). Similarly, ODQ enhanced vasorelaxation to PPIX yet impaired the response to DEA/NO (control pEC_{50} = 7.24 ± 0.11 vs ODQ pEC_{50} = 5.68 ± 0.08, n = 5–10, $P < 0.0001$). Zn-PPIX (3&10 μM), an inhibitor of heme-free sGC, caused a concentration-dependent right-ward shift in the relaxation response to BAY 58–2667 such that the potency was decreased 30- ($P = 0.0001$, n = 6) and 3000-fold ($P < 0.0001$, n = 6), respectively. The response to PPIX (pEC_{50} = 5.31 ± 0.57, R_{max} = 55.5 ± 5.8%) was abolished in the presence of 3 μM Zn-PPIX ($P < 0.0001$) yet vasorelaxation to DEA/NO was unchanged. The peroxynitrite donor, SIN-1 (1 mM) decreased the sensitivity to DEA/NO 15-fold ($P = 0.0003$, n = 4) yet the response to BAY 58–2667 was unaffected.

Conclusion

The vasodilator efficacy of BAY 58–2667 and PPIX in small mesenteric arteries suggests that a relatively enhanced pool of oxidized/heme-free sGC exists in the resistance vasculature under physiological conditions and this pool may be increased during oxidative stress and in the absence of endogenous NO. This establishes sGC activation as a novel pharmacological approach for both disease- and region-specific vasodilator therapy.