BMC Pharmacology

Poster presentation

Open Access

Antihypertrophic actions of NO-independent soluble guanylyl cyclase (sGC) ligands BAY 41-2272 and BAY 58-2667 *in vitro*

Rebecca Ritchie*[1], Jennifer Irvine[1], Jane Love[1], John Horowitz[3], Johannes-Peter Stasch[4] and Barbara Kemp-Harper[2]

Address: [1]Heart Failure Pharmacology, Baker IDI Heart & Diabetes Institute, Melbourne, Vic 8008, Australia, [2]Department of Pharmacology, Monash University, Clayton, Vic 3800, Australia, [3]Cardiology Unit, The Queen Elizabeth Hospital, Woodville, SA 5011, Australia and [4]Bayer HealthCare AG, Pharma Research Center, Aprather Weg 18a, 42096, Wuppertal, Germany

Email: Rebecca Ritchie* - rebecca.ritchie@bakeridi.edu.au

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P59 doi:10.1186/1471-2210-9-S1-P59

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P59

Background

Over the last decade, we have shown that cGMP, derived from bradykinin, nitric oxide (NO•, both from endogenous and exogenous sources) or natriuretic peptides, is a potent inhibitor of cardiac hypertrophy, across isolated cardiomyocytes and intact hearts both *ex vivo* and *in vivo*. However, NO• bioavailability is reduced due to scavenging by ROS; furthermore, oxidation of sGC may result in sGC dysfunction (including loss of responsiveness to NO•). In the present study, we tested the hypothesis that the NO•-independent sGC stimulator BAY 41-2272 and the NO-independent sGC activator BAY 58-2667 elicit powerful antihypertrophic actions.

Materials and methods

Neonatal rat cardiomyocytes were incubated at 37°C in the presence of the hypertrophic stimulus, endothelin-1 (ET_1, 60 nM) ± BAY 41-2272 or BAY 58-2667 (0.01–0.3 μM) for 48 h in serum-free conditions. Cardiomyocyte hypertrophy was assessed in live cells using conventional *in vitro* markers of hypertrophy, two dimensional area and cardiomyocyte *de novo* protein synthesis. Results were expressed as % paired control cardiomyocytes, mean ± SE.

Results

See Table 1.

Conclusion

These results provide evidence that BAY 41-2272 and BAY 58-2667 elicit concentration-dependent inhibition of cardiac hypertrophy *in vitro*, in the absence of confounding haemodynamic factors and even at low (submicromolar) concentrations. These novel NO•-independent sGC ligands thus potentially may serve as useful antihypertrophic agents in patients, independent of blood pressure.

Table 1: sGC ligands inhibit cardiomyocyte hypertrophy

	Control	ET_1 alone	ET_1 + BAY (0.01 μM)	ET_1 + BAY (0.03 μM)	ET_1 + BAY (0.10 μM)	ET_1 + BAY (0.30 μM)
Cell size (% paired control cardiomyocytes, both n = 4)						
BAY 41-2272	100 ± 0%	146 ± 9%*	128 ± 5%#	116 ± 7%#	106 ± 6%#	108 ± 6%#
BAY 58-2667	100 ± 0%	141 ± 8%*	133 ± 11%	123 ± 7%#	113 ± 2%#	108 ± 12%
De novo protein synthesis (% paired control cardiomyocytes, n = 5–6)						
BAY 41-2272	100 ± 0%	122 ± 1%*	102 ± 1%#	101 ± 1%#	102 ± 2%#	110 ± 0%#
BAY 58-2667	100 ± 0%	135 ± 2%*	110 ± 3%	117 ± 3%	107 ± 2%#	108 ± 3%

*$p < 0.05$ versus control; #$p < 0.05$ versus ET_1, on one-way RM. DMSO, the vehicle for the sGC ligands, had no effect on either parameter either alone, or in the presence of ET_1.