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Role of activators of ferric sGC in cardiovascular disease

Ursula Schindler*[1], Martina Klein[1], Wolfgang Linz[1], Hartmut Rütten[1], Stefan Schäfer[1], Hartmut Strobel[1], Andreas Schäfer[2], Johann Bauersachs[2], Sven Wassmann[3] and Martin van Eickels[1]

Address: [1]Aventis Pharma Deutschland GmbH, Group sanofi-aventis, Frankfurt, Germany., [2]Medizinische Klinik I, Universitätsklinikum, Würzburg, Germany. and [3]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany.

Email: Ursula Schindler* - Ursula.Schindler@sanofi-aventis.com

* Corresponding author

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Soluble guanylyl cyclase (sGC), the key transducer of nitric oxide (NO) signalling in vascular smooth muscle cells and platelets, exists in two redox forms: the NO-sensitive ferrous heme-iron (Fe(II)) form and a NO-insensitive oxidized form containing the ferric heme-iron (Fe(III)). HMR1766 (proposed INN ataciguat sodium) reversibly stimulates the oxidized form of sGC (crude and purified) in various species and organs to about 10 to 30 % of the maximal activity achieved with NO donors. Acute treatment with HMR1766 has anti-ischemic (acute coronary stenosis) and anti-thrombotic (coronary thrombosis) effects in dog models at doses that did not influence arterial blood pressure or other hemodynamic parameters.

However, the role of oxidized sGC under chronic pathophysiological conditions is poorly understood. We therefore investigated the chronic activation of the oxidized sGC by HMR1766 as a therapeutic strategy to inhibit vascular and endothelial dysfunction, myocardial hypertrophy and survival in various animal models.

Compared to wild-type mice, placebo-treated apolipoprotein-deficient ($ApoE^{-/-}$) mice fed with a high fat diet develop endothelial dysfunction, as indicated by an impaired endothelium-dependent vasodilatation, and severe atherosclerotic lesion formation in the aorta. Long-term treatment with HMR1766 containing chow (6 and 15 weeks) significantly reduced atherosclerotic plaque formation and markedly improved endothelium-dependent vasodilatation.

Diabetes mellitus is associated with an increased thromboembolic risk via activation of circulating platelets as well as the development of endothelial and vascular dysfunction. Both effects have been attributed to a lack of nitric oxide (NO) bioavailability and/or reduced sensitivity of sGC for NO. A single intravenous injection of streptocotozine (STZ) to rats induced type-I diabetes and attenuated NO-stimulated sGC activity isolated from aorta as compared to the placebo injected control group. The HMR1766-stimulated sGC activity was not different between both groups. Chronic treatment of STZ diabetic rats with HMR1766 starting 2 weeks after STZ normalized platelet activation as measured by a reduction of P-selectin expression and an increase in platelet vasodilator-stimulated phosphoprotein (VASP)-phosphorylation. Activation of sGC by HMR1766 normalized vascular dysfunction (sensitivity of vascular smooth muscles to constrictors) and restored endothelium-dependent relaxation in isolated aortic rings from control and placebo-treated STZ rats.

Spontaneously hypertensive rats (SHR) develop endothelial dysfunction (impairment of endothelium-dependent relaxation) and begin to die from cardiovascular complications at approximately 15 months of age. Long-term treatment with HMR1766 starting at the age of 15 months significantly improved endothelial dysfunction in isolated aortic rings from control and placebo-treated SHR and significantly extended lifespan.

The NO-cGMP pathway also plays a pivotal role in the pathogenesis of pulmonary arterial hypertension (PAH).

Four weeks after a single injection of monocrotaline, which induces pulmonary arterial endothelial injury, rats develop progressive pulmonary hypertension, with severe right ventricular hypertrophy and mortality of more than 50% within 4–6 weeks. HMR1766, chronically administered after the onset of PH (day 14 to 28), reduced right ventricular pressure, right ventricular hypertrophy and significantly improved survival.

In conclusion, the present data obtained with HMR1766, which activates preferably the oxidized form of sGC, suggest an important role of oxidized sGC in endothelial, vascular and thrombocyte dysfunction. Chronic HMR1766 treatment improves endothelial function and reduces atherosclerosis in ApoE$^{-/-}$ mice, normalizes platelet activation and restores endothelial and vascular function in type-I diabetic rats, improves endothelial dysfunction and survival in old SHR, and improves vascular remodelling, hemodynamics and survival in rats with pulmonary hypertension. Therefore, HMR1766 represents a promising agent for prevention and treatment of atherosclerosis and pulmonary hypertension.