| | Route of administration | Experimental model | The effects | Ref. |
|---|---|---|---|---|
| **rhACE2** | Preincubation | *Iin vitro,* HUVECs | • increased NO contents in cell culture medium and the expression level of eNOS<br>• the involvement of PI3K/AKT signaling pathway in rhACE2's promotion of the activity of endothelial cell eNOS | [62] |
| | Chronic (2 weeks), orally | Wild type C57BL/6 mice infused with Ang II | • reduced Ang II-induced hypertrophy and diastolic dysfunction<br>• antagonized Ang II-mediated myocardial fibrosis<br>• increased Akt and eNOS expression | [60] |
| | Chronic (2 weeks), intraperitoneally | Model of atherosclerosis, apolipoprotein E knockout mice, ACE2 knockout mice, ApoE/ACE knockout mice infused with Ang II | • increased in renal ACE2 and nephrin levels<br>• reversed Ang II-induced renal inflammation, superoxide generation, kidney dysfunction and adverse renal injury | [61] |
| **Xanthenon** | Acute, intravenously Chronic (4 weeks), osmotic minipump implanted subcutaneously | WKY and SHR rats | • especially in SHRs: a fall in arterial blood pressure and heart rate and increased response to bradykinine<br>• inhibition of perivascular and renal fibrosis in SHRs | [64] |
| | | *In vitro,* isolated heart | • improvement of hemodynamic parameters<br>• inhibition of myocardial fibrosis in the SHRs | |
| | Chronic (4 weeks), osmotic minipumps implanted subcutaneously | Monocrotaline-induced pulmonary hypertension in rats | • decreased right ventricular systolic pressure<br>• attenuation of interstitial fibrosis<br>• attenuation of increases in the levels of TGFβ (transforming growth factor beta), TNFα (tumor necrosis factor alpha), IL-1 (interleukin-1), IL-6 (interleukin-6), MCP-1 (monocyte chemotactic protein 1), NF-κB (nuclear factor-kappa B)<br>• increased anti-inflammatory IL-10 (interleukin-10) level | [65] |
| | Acute, intravenously | $FeCl_3$ – induced venous thrombosis in WKY and SHR rats, mice | • decreased thrombus weight<br>• prolongation of the time needed for thrombus formation<br>• reduction in thrombus area | [66] |
| | Chronic (4 weeks), osmotic minipumps implanted subcutaneously | WKY and SHR rats | • decreased cardiac collagen content<br>• reduction in ERK phosphorylation<br>• no change in cardiac AT1 protein levels | [67] |
| | Chronic (30 days), orally | Streptozotocin-induced diabetic rats | • improvement of cardiovascular autonomic dysfunction in diabetes (an increase in the baroreflex bradycardia sensibility and in the chemoreflex chronotropic response) | [68] |
| **DIZE** | Chronic (2-4 weeks), orally | Monocrotaline-induced pulmonary hypertension in rats | • inhibition of the pulmonary hypertension development<br>• decreased inflammatory cytokines level<br>• improved pulmonary vasoreactivity<br>• enhanced cardiac function | [69] |

| | | | | |
|---|---|---|---|---|
| | Acute, intravenously Chronic (4 weeks), orally Preincubation | Normotensive Wistar rats, 2K1C renovascular hypertensive rats, isolated aortic rings | • decrease in BP with a compensatory increase in HR in nornotensive rats<br>• decrease in BP In 2K1C rats<br>• prevented the development of cardiac hypertrophy induced by hypertension<br>• the involvement of Mas activation and NO release in the vasodilator effects of DIZE | [70] |
| | Acute (3 days), intravenously | Model of renal ischemia/ reperfusion injury in rats | • decrease in blood urea nitrogen, creatinine, liver functional indices, serum malondialdehyde<br>• increase in kidney nitrite levels<br>• increase in creatinine and decrease in serum nitrite levels in female rats | [71] |
| | Chronic (3 weeks), subcutaneously | Model of atherosclerosis, apolipoprotein E knockout mice with erectile dysfunction | • improved hypercholesterolemia-induced corpus carvenosum (CC) injury<br>• decreased collagen content within the CC<br>• reduced ROS production and NADPH oxidase expression, and elevated nNOS and eNOS expression and NO bioavailability in the penis of ApoE(-/-) mice | [72] |
| | Chronic (30 days), orally | Male mice | • lowered body weight, serum cholesterol and triglycerides, epididymal and retroperitoneal adipose tissue weights<br>• increased epididymal ACE2 and decreased ACE and angiotensinogen expression<br>• decreased adipogenesis-related gene transcription, such as ACC and FAS mRNA | [73] |

**Table 2. rhACE2 and ACE2 activators in the experimental studies.**