Proceedings of German Society for Stem Cell Research (PGSSCR)

Growth hormone treatment improves markers of systemic nitric oxide bioavailability via the insulin-like growth factor-1
Importance for endothelial progenitor cells

Thum T, Fleissner F, Klink I, Tsikas D, Stichtenoth DO, Ertl G, Bauersachs J

Julius-Maximilians University, Internal Medicine I / Cardiology, Wurzburg, Germany
Medical School Hannover, Clinical Pharmacology, Hannover, Germany

Published online on 16 May 2007

Introduction:
Growth hormone (GH) treatment of GH-deficient patients improves endothelial function and reduces overall cardiovascular risk. Mechanistically, the GH-dependent insulin-like growth factor-1 (IGF-1) stimulates activity of the endothelial NO synthase, which regulates in part vasoprotective endothelial progenitor cells (EPC). Low IGF-1 and EPC concentrations in patients have recently been correlated with impaired vascular function and development of coronary artery disease.

Materials and Methods:
Here we tested our hypothesis, that treatment with recombinant human (rh) GH increases NO bioavailability and subsequently augments circulating EPC levels in healthy male volunteers (mean age 57.4 ± 1.4 years; n=16). We measured markers of NO bioavailability, such as cyclic guanosine monophosphate (cGMP), vascular endothelial growth factor (VEGF), nitrate, nitrite and asymmetric dimethylarginine (ADMA) as well as EPC numbers and blood pressure before and after a ten day treatment of 0.4 mg rhGH/per day.

Results:

rhGH treatment increased levels of IGF-1 by 2-fold (p<0.0001) and of the IGF-1 binding protein 3 by 19%±2.7% (p<0.001). Concentrations of the sensitive NO mediator cGMP (12.69±1.04 vs 14.79±1.00 µM cGMP/mM creatinine; p=0.03) and of VEGF (19.0±1.0 vs 21.4±1.4 pg/ml; p<0.05) were increased after rhGH treatment. In contrast, plasma concentrations of the endogenous NOS inhibitor ADMA were reduced (p<0.05), whereas plasma nitrate levels tended to be increased. The rise in NO bioavailability was closely correlated with a 2-fold increase in circulating CD133+/VEGFR2+ EPC. These findings were also observed in mice treated with GH for 7 days. Importantly, blocking of the IGF-1 receptor in vivo abolished the GH-mediated effects on markers of increased NO bioavailability.

Discussion and Conclusions:
In healthy middle-aged subjects rhGH treatment enhances overall nitric oxide bioavailability and subsequently EPC numbers. Animal data demonstrate increased NO availability to be mediated via an increase in IGF-1 plasma levels. Our proof-of-principle
study warrants further clinical trials to test a potential therapeutic effect of recombinant human GH in patients with various cardiovascular diseases, impaired NO bioavailability and EPC.