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NOS inhibitors synchronize calcium oscillations in fat-derived mesenchymal stem cells by increasing gap junctional coupling

Sauer H, Hatry M, Steffen P, Wartenberg M

Justus-Liebig-University Giessen, Aulweg 129, 35392 Giessen, Germany

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Fat-derived mesenchymal stem cells are a promising source of stem cells for cell transplantation. In the present study it is shown that undifferentiated human fat-derived stem cells display robust oscillations of intracellular calcium $[Ca^{2+}]_i$ which may be associated with differentiation processes. $[Ca^{2+}]_i$ oscillations were dependent on extracellular calcium and calcium release from intracellular stores since they were abolished in calcium-free medium and in the presence of the store-depleting agent thapsigargin. $[Ca^{2+}]_i$ oscillations were apparently regulated by the inositol 1,4,5-trisphosphate (InsP3) pathway and dependent on gap junctional coupling since they were abolished in the presence of the phospholipase C antagonist U73,122, in the presence of the InsP3 receptor antagonist 2-aminoethoxydiphenyl borate (2-APB) as well as in the presence of the gap junction uncouplers 1-heptanol and cabenoxolone. Preincubation with the nitric oxide (NO) synthase inhibitors NG-monomethyl-L-arginine (L-NMMA), N(G)-nitro-L-arginine methyl ester (L-NAME), and diphenyl iodinium (DPI), synchronized $[Ca^{2+}]_i$ oscillations between individual cells within the area of inspection, whereas the NO-donor S-

nitroso-N-acetylpenicillamine (SNAP) and sodium nitroprusside (SNP) were without effects. The synchronization of $[Ca^{2+}]_i$ oscillations was due to an improvement of intracellular coupling since fluorescence recovery after photobleaching (FRAP) experiments revealed increased reflow of the fluorescence indicator calcein into the bleached area in the presence of the NOS inhibitor DPI. In summary our data demonstrate that intracellular NO levels regulate synchronization of $[Ca^{2+}]_i$ oscillations in undifferentiated fat-derived stem cells by controlling gap junctional coupling.

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