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Conclusion: Age is an important factor to modulate human vascular smooth muscle cell proliferation, rather than apoptosis. The effect of age is stronger than the one exerted by the antidiabetic drug pioglitazone. This finding may be important to design future age-tailored antiproliferative treatments for proliferative vascular diseases.
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P08-01
EFFECT ANTI-CD44 AND ANTI-CD62L ON HUMAN ENDOTHELIAL PROGENITOR CELLS: IMPLICATIONS FOR AN ALTERED VASCULAR FUNCTION IN CHRONIC MYELOPROLIFERATIVE NEO

Ramajo M.[1], *Redondo S.*[1], *Navarro-Dorado J.*[1], *Ostos F.*[1], *Martínez J.*[2], *Gallardo M.*[2], *Barrio S.*[2], ***Reguillo F.***[3], *Tejerina T.*[1]

[1]Department of Pharmacology, School of Medicine, Universidad Complutense, Madrid, Spain; [2]Service of Haematology, Hospital 12 de Octubre, Madrid, Spain; [3]Service of General Surgery, Hospital Clínico San Carlos, Madrid, Spain

Introduction: Myeloproliferative neoplasms are chronic neoplasic disorders where an increased cardiovascular mortality takes place. Several studies link endothelial progenitor cell (EPC) dysfunction with vascular dysfunction and thrombosis. On the other hand, the cell adhesion molecules CD44 and CD62L have been shown to be upregulated in patients with myeloproliferative neoplasms.
Material and Methods: EPCs were cultured from peripheral blood mononuclear cells from healthy donors by using the early-outgrowth protocol and cultured on fibronectin-coated 6-well plates. Medium (MV-II microvascular) was changed at day 4 and number of colony forming units (CFU) was assessed at day 7. For the last 72 h, some cells were coincubated with anti-CD44 or anti-CD62L at 10 mcg/ml each one. Proliferative rate was assessed by a BrdU proliferation kit.
Results: Antibodies dramatically increased the number of CFU per plate from 3.5 (control) to 755 (anti-CD44) and 23.6 (anti-CD62L). However, they did not change the proliferative rate at a significant extent.
Conclusion: Although CD44 and CD62L have been implicated in hematopoietic stem cell survival, their inhibition increases CFUs in EPC cultures. Thus, these two molecules may mediate the EPC dysfunction that has been described in chronic myeloproliferative neoplasms and subsequent cardiovascular disease.
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P09-01
EFAVIRENZ INDUCES LEUKOCYTE RECRUITMENT *IN VIVO* THROUGH MAC-1/ICAM-1 INTERACTION

Orden S.[1], *de Pablo C.*[1], *Esplugues J. V.*[1,2], *Alvarez A.*[1,2]

[1]Departament of Pharmacology, Faculty of Medicine, University of Valencia, Valencia, Spain; [2]Center for Biomedical Research Network: Digestive and Liver Diseases (CIBERehd)

Introduction: Highly active antiretroviral therapy (HAART) has been linked to the development of cardiovascular diseases. Efavirenz (EFV) is one of the most widely used antiretroviral agents, and thus cannot be ruled out as a causal agent of these side effects. We have demonstrated that EFV promotes leukocyte accumulation *in vitro* through Mac-1/ICAM-1 interaction. The present study was designed to confirm our data *in vivo*.
Methods: Leukocyte rolling, adhesion and emigration in mesenteric venules of anaesthetized rats were monitored using intravital microscopy. These parameters were determined 4 h after intraperitoneal administration of clinically relevant doses of EFV (15 μM) or methanol (vehicle). Adhesion molecules involved in EFV-induced responses were determined by intravenous pre-treatment of animals with antibodies directed against rat Mac-1 (CD11b/CD18) or its endothelial ligand ICAM-1 (CD54). A one-way ANOVA + Newman-keuls analysis was performed, and statistical significance was **P < 0.01 (vs. vehicle), n?4 animals.
Results: Administration of EFV promoted a significant increase in leukocyte rolling flux (62.8 ± 4.2 vs. 29.8 ± 4.4**), adhesion (8.8 ± 0.8 vs. 2.0 ± 0.4**) and emigration (7.0 ± 1.1 vs. 0.6 ± 0.2**) with respect to that observed in vehicle-treated animals. Blocking antibodies against both subunits of Mac-1 (CD11b and CD18) or ICAM-1 (CD54) prevented the leukocyte recruitment induced by this drug.
Conclusion: Acute exposure to EFV induces leukocyte-endothelial cell interactions in rat mesenteric microvenules at clinically relevant doses *in vivo*. This process is mediated by the ß2 integrin Mac-1, which interacts with its endothelial ligand ICAM-1. These results suggest that EFV is involved in the genesis of the cardiovascular diseases observed in HA-ART-treated patients.

P10-01
EPICATECHIN RESTORE ENDOTHELIAL FUNCTION IN DOCA-SALT HYPERTENSION: ROLE OF ENDOTHELIN-1, NADPH OXIDASE AND NRF2 PATHWAYS

Gómez-Guzmán M.[1], *Jiménez R.*[1], *Sánchez M.*[1], *Zarzuelo M. J.*[1], *Galindo P.*[1], *Quintela A. M.*[1], *Romero M.*[1], *Tamargo J.*[2], *Pérez-Vizcaíno F.*[2], *Duarte J.*[1]

[1]Department of Pharmacology, School of Pharmacy, University of Granada, Granada, Spain; [2]Department of Pharmacology, School of Medicine, University Complutense of Madrid, Madrid, Spain

Introduction: Flavanols-rich diets have been reported to exert beneficial effects in preventing cardiovascular diseases , such as hypertension. Our present study was designed to examine whether chronic intake of epicatechin, the main dietary flavanol, prevents the DOCA-salt-induced hypertension and endothelial dysfunction.
Material and Methods: Rats were randomly divided into five groups: control, (−)-epicatechin (EPI10, 10 mg/kg), DOCA-salt, DOCA-salt-EPI2 (2 mg/kg) and DOCA-salt-EPI10 (10 mg/kg). Rats were daily administered by gavage for 5 weeks.
Results: The high dose of epicatechin prevented both the increase in systolic blood pressure and proteinuria induced by DOCA-salt. Plasma endothelin-1 and malondialdehyde levels and urinary isoprostaglandin F2alfa excretion, were found to be increased in animals of DOCA group. Epicatechin 10 mg/kg treatment reduced these parameters in DOCA-salt rats, having no effects on control rats. Aortic superoxide levels was enhanced in DOCA-salt group and abolished by both doses of epicatechin. However, only epicatechin 10 mg/kg reduced the raise in aortic nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase activity and aortic p47phox and p22phox gene overexpression found in DOCA-salt animals. Epicatechin increased the transcription of nuclear factor-E2-related factor-2 (Nrf2) and Nrf2 target genes in aortas from control and DOCA-salt rats. Epicatechin also improved the blunted endothelium-dependent relaxation to acetylcholine in phenylephrine precontracted aortic rings and increased the phosphorylation of both Akt and eNOS.
Conclusion: All these results suggest that a chronic treatment with epicatechin prevents hypertension and vascular dysfunction. Epicatechin prevent vascular oxidative stress by reducing ET-1 release, inhibiting NADPH oxidase activity and increasing Nrf2-drived antioxidant defences.

P11-01
IMPLICATION OF EXTRACELLULAR SIGNAL-REGULATED KINASE IN THE ACTIVATION OF HEAT SHOCK PROTEIN 27 OBSERVED AFTER NALOXONE-INDUCED MORPHINE WITHDRAWAL IN THE RAT HEART

González-Cuello A.[1], *Martínez-Laorden E.*[2], *Milanés M. V.*[2], *Laorden M. L.*[2], *Almela P.*[2]

[1]Department of Nursing, University of Murcia, Murcia, Spain; [2]Department of Pharmacology, Faculty of Medicine, University of Murcia, Murcia, Spain

Introduction: Different drugs of abuse, such as morphine and/or its withdrawal , induce severe cellular stress situations that can cause a sudden change in the cellular environment, to which the cell is not prepared