Cutaneous iontophoresis of treprostinil, a prostacyclin analogue, increases microvascular blood flow in diabetic malleolar area

Wild-type (WT) and obese (ob/ob) mice were assigned to control NaCl 0.9% was performed in the malleolus area. Skin hyperaemia was quantified using non-invasive laser speckle contrast imaging, and expressed as cutaneous vascular conductance (CVC).

Results: In healthy controls and diabetic patients, treprostinil 250 μg induced a significant increase in CVC compared with NaCl (for diabetic patients, AUC0-4 h + 16.181 ± 6.709% vs. 2219 ± 3616% BL.min, respectively; P = 0.002). In both groups, peak hyperaemia was obtained between 10 min and 1 h after the end of treprostinil iontophoresis and flow remained higher than baseline up to 6 h. No side-effects were reported. Topical administration of prostacyclin analogue administered through iontophoresis combines the advantages of drug therapy and local low-intensity current application providing a potential innovative, well-tolerated therapy of microvascular skin ulcers. Treprostinil cathodal iontophoresis should be further investigated as a novel local therapy for diabetic ulcers.

Discussion/Conclusion: Cutaneous iontophoresis of 250 μg treprostinil increases microvascular blood flow in malleolar area in healthy volunteers and diabetic patients, without inducing systemic or local side-effects. Topical administration of prostacyclin analogue administered through iontophoresis combines the advantages of drug therapy and local low-intensity current application providing a potential innovative, well-tolerated therapy of microvascular skin ulcers. Treprostinil cathodal iontophoresis should be further investigated as a novel local therapy for diabetic ulcers.

CO-004

Chronic oral intake of a standardized Crataegus extract prevents hypertension-induced endothelial dysfunction and renal structural changes in rats: Role of oxidative stress

T Ribeiro1, C Auger2, Q Jabene3, G Silva4, IA Medeiros5, N Boem6, L Monassie7, VB Vanholder8 and M Renoux9

1 Orsay University, Medical University, Gdansk, Poland; 2 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 3 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 4 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 5 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 6 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 7 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 8 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France); 9 Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France)

Introduction: Oral intake of a standardized Crataegus extract group for 6 weeks. Illkirch (France); 10 Joao Pessoa (Brazil); 11 Grenoble (France); 12 Cr. Clinical Pharmacology Department, Inserm CIC1406, Grenoble University Hospital, Grenoble (France).

Results: In healthy controls and diabetic patients, treprostinil 250 μg induced a significant increase in CVC compared with NaCl (for diabetic patients, AUC0-4 h + 16.181 ± 6.709% vs. 2219 ± 3616% BL.min, respectively; P = 0.002). In both groups, peak hyperaemia was obtained between 10 min and 1 h after the end of treprostinil iontophoresis and flow remained higher than baseline up to 6 h. No side-effects were reported. Topical administration of prostacyclin analogue administered through iontophoresis combines the advantages of drug therapy and local low-intensity current application providing a potential innovative, well-tolerated therapy of microvascular skin ulcers. Treprostinil cathodal iontophoresis should be further investigated as a novel local therapy for diabetic ulcers.

Discussion/Conclusion: Cutaneous iontophoresis of 250 μg treprostinil increases microvascular blood flow in malleolar area in healthy volunteers and diabetic patients, without inducing systemic or local side-effects. Topical administration of prostacyclin analogue administered through iontophoresis combines the advantages of drug therapy and local low-intensity current application providing a potential innovative, well-tolerated therapy of microvascular skin ulcers. Treprostinil cathodal iontophoresis should be further investigated as a novel local therapy for diabetic ulcers.

CO-005

M3 receptor as a key target of N,N-diethyl-m-toluamide (DEET) to promote angiogenesis

S Bhattacharjee, N Cleere, V Aïp-Marchais1, B Lapied2, R ANDRIANTSOITAIBA1, S Faure1

1 INSERM U1063, Stress Oxidant et Pathologies Métaboliques (SOPAM), Université d’Angers – Angers (France); 2 UPRès EA 2647 Récepteurs et Canaux ioniques, Molécules membranaires (RCoMM), Montpellier universitaires de Montpellier (UMU), Montpellier (France)

Introduction: It has been suggested that muscarinic pathway can lead to proangiogenic effects in endothelial cells. The insect repellent N,N-diethyl-m-toluamide (DEET) recently proved to act as an inhibitor of human acetylcholinesterase has been reported to correlate tumor development. As angiogenesis is a criti-
Arthritis score was daily evaluated. At the end of treatment, endothelial bacterium butyricum in the tail of male Lewis rats. At the first signs of arthritis, the pro-angiogenic properties of DEET in both in vitro and in vivo conditions. DEET also potentiates carbasho-induced calcium signaling in HEK/M1. Moreover, tumorigenesis following U87MG cells injection in Nude mice was increased by administration of DEET due to enhanced tumor microvascular density.

Discussion/Conclusion: These data emphasize the potential role of DEET as a pro-angiogenic toxic, via the involvement of M3 muscarinic receptor subtype that could explain its potentiating effect on tumor development [1-3].


CO-006
Etanercept improves endothelial function in Rat Adjuvant-Induced Arthritis: mechanisms involved
P Tottono1, K Maguin-Gate2, A Mommier2, A Tessler3, C Marie3, C Prat4, C Mougel1, A Monnier1, A Tessier3, C Marie3, C Prat4, C Mougel1, A Monnier1

Introduction: Growing evidence indicate that increased cardiovascular risk associated to Rheumatoid Arthritis (RA) is secondary to the presence of endothelial dysfunction (ED) [1]. To date, the effect of anti-arthritic drugs used on RA-induced ED is still controversial [2-3]. In the present study, we investigated the effect of the anti-TNFα Etanercept on endothelial function in the model of adjuvant-induced arthritis (AIA) rats.

Material and methods: AIA was induced by an intradermal injection of Mycobacterium butyricum in the tail of male Lewis rats. At the first signs of arthritis, AIA rats received Etanercept (10 mg/kg/ 3 days, s.c.) or saline (control) (AIA) rats for 21 days. Arthritis score was daily evaluated. At the end of treatment, endothelial function was studied in pre-constricted aortic rings relaxed by cumulative concentration of acetylcholine (Ach, 10–11 to 10–4 M) or not of inhibitors of NOS (LNAME, COX-2, NS398), Arginine (nor-NOHA), EDHF (apamin/charybdotoxin) and superoxide anion production (Tempo). Ach response was expressed as the percent of relaxation (%R) of COX-2, Arginin2, p22phox and p47phox expression was evaluated by western blotting. Results: As compared to control AIA, Etanercept significantly reduced arthritis score [20% (P < 0.001)] and the effect was associated with a significant improvement of Ach-induced relaxation (P < 0.05). No correlation was found between the arthritis score and Ach-induced relaxation (rmax = 0.195; P = 0.246, all rats). The results showed that the beneficial effect of Etanercept relied on increase in NOS activity and a decrease in COX-2 and Argininase activities as well as PO2 production. These effects are secondary to increased eNOS expression and phos- phorylation and decreased COX-2. Argininase-2 and p22phox expressions. By contrast, EDHF production and p47 expression were unaffected by the treatment.

Discussion/Conclusion: Our data demonstrated that Etanercept improved endothelial function in AIA, via an impact on the NOS, Argininase-COX-2 and NADPH oxidase pathways. The lack of correlation between endothelial function and arthritis score in AIA suggests that improved endothelial function evolution by Etanercept is independent of the reduction of systemic inflammation but rather related to direct vascular effects.

References:

CO-007
Imidazoline-like drug improve insulin sensitivity through a direct stimulation of adiponectin secretion in primary adipocytes
M Weiss, F Traversi, P Bousquet, H Greney, N Niederhofer Laboratoire de Neurobiologie et de Psychopharmacologie, U1093 “Cognition, Action et Plasticité”, UFR Santé de Strasbourg – Strasbourg (France)

Introduction: Altered adiponectin (a major insulin sensitizer adipokine) signal- ing has been proposed as a key factor in the development of insulin resistance and thus, in the pathogenesis of metabolic syndrome. We previously showed that mimicking a pyridine receptor (I/P) ligand can improve insulin sensitivity (SI) and glucose tolerance partly through increased adiponectin plasma levels. The objective of the present study was to explore possible direct actions of I/P ligands on adipocytes.

Materials and Methods: Experiments were carried out on rat adipocytes isolated from the epidymal white adipose tissue of aged male Wistar rats. Expression of I/P on adipocytes was verified with competition binding assays using [125I] pyridinoline as radioligand. In order to determine the ED50 of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten. In order to determine the impact of the potential pro-angiogenic secretory profile, primary adipocytes were treated with increasing concentrations of LNP509, an I/P ligand, in the presence or not of the I/P antagonist efaxoten.