BELGIAN SOCIETY OF FUNDAMENTAL AND CLINICAL PHYSIOLOGY AND PHARMACOLOGY

Spring Meeting

Saturday, March 7 2009

A B S T R A C T B O O K

organisation

Prof. Dr. R. Lefebvre
Universiteit Gent
Vakgroep Farmacologie
Heymans Instituut
De Pintelaan 185 (Blok B)
9000 GENT

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UNIVERSITEIT GENT
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Main lecture
(aud. E – Blok B)

10.00-10.45 Dr. Roberto MOTTERLINI
(Department of Drug Discovery and Development – Italian Institute of Technology – Genova Italy):

Carbon monoxide releasing molecules: anti-ischaemic and anti-inflammatory effects.

Oral Communications

Fundamental Physiology and Pharmacology
aud. E – Blok B

11.00-11.15 O. DE BACKER, E. ELINCK, R.A. LEFEBVRE (UGent)
Peroxisome proliferator-activated receptor γ (PPAR γ) activation alleviates postoperative ileus by inhibition of Egr-1 expression and its downstream target genes.

11.15-11.30 A.L. DEITEREN[1], B.Y. DE WINTER[1], M.G. ZIZZO[2], P.A. PELCKMANS[1], J.G. DE MAN[1] ([1]UAntwerp & [2]Univ. Palermo, Italy)
Functional study on the role of tachykinins in colonic peristaltic activity in mice.

11.30-11.45 K. DECALUWE, S. NIMMEGEERS, R. THOONEN, P. BROUCKAERT, J. VAN DE VOORDE (UGent)
In vitro and in vivo studies on the importance of the soluble guanylyl cyclase alpha 1 subunit in penile erection.

11.45-12.00 S. BARON, F. WUYTACK, L. RAEYMAEKERS, J. VANOEVELEN (KULeuven)
The secretory pathway Ca^{2+}-ATPase 1 (SPCA1) is localized in cholesterol-rich domains of human carcinoma cells.

12.00-12.15 Bullet Session
Oral presentations of posters n° 1,2,3,4

Clinical Pharmacology
Room Heymans Foundation – 1st floor Blok B

11.00-11.15 J. DE SMET, K. BOUSSERY, M. VAN WINCKEL, P. DE COCK, P. DE PAEPE, J.P. REMON, J. VAN BOCXLAER (UGent)
Pharmacokinetic study of omeprazole Multi-Unit Pellet System (Losec MUPS®) versus extemporaneous bicarbonate formulation in patients with cerebral palsy and mental retardation.

11.15-11.30 J. DE GREVE, E. TEUGELS, D. GALDERMANS, J. DE MEY, P. IN 'TVELD, C. GEERS, L. DECOSTER, D. SCHALLIER, M. TATON, M. SHAHIDI (VUBrussel)
An irreversible dual inhibitor of EGFR and HER2 in biomarked adeno-carcinoma of the lung.

11.30-11.45 I. FABRY, P. DE PAEPE, L. VAN BORTEL (UGent)
Influence of tocolytics on central and peripheral hemodynamics.

11.45-12.00 K. ALLEGAERT, R. VERBESSELT, G. NAULAERS, J. DE HOON (KULeuven)
Is propofol the perfect hypnotic agent for procedural sedation in neonates?

12.00-12.15 T. DE BACKER, R. VANDER STICHELE, L. VAN BORTEL (UGent)
Benefit risk assessment of older products.

12.15-12.30 R. VANDER STICHELE[1], M. ELSEVIERS[2] ([1]UGent, [2]UAntwerp)
Medical prescribing for institutionalized demented patients.

Fundamental physiology and pharmacology
aud. E – Blok B

Oral Comunications

13.30-13.45 S. KOULCHITSKY, O. WAROUX, J.F. LIEGEOIS, V. SEUTIN (ULiège)
Telemetric recordings of midbrain dopaminergic neurons in awake and freely moving rats.

13.45-14.00 P. ALIX, V. SEUTIN (ULiège)
Characterization of a SK-mediated medium duration afterhyperpolarization in Dorsal Raphe Neurons.

14.00-14.15 D. DE BUNDEL[1], E. LOYENS[1], F. KIAGADAKI[2], N. AOURZ[1], B. STRAGIER[1], Y. MICHOTTE[1], K. THERMOS[2], I. SMOLDERS[1]
([1] VUBrussel & [2] Univ. Creta Heraklion (Greece)
Investigations into the role of somatostatin in the anticonvulsive effects of insulin-regulated aminopeptidase inhibitors.

14.15-14.30 P. PLAZA[1], I. CUEVAS[1], O. COLLIGNON[1], C. GRANDIN[2], A.G. DE VOLDER[1], L. RENIER[1] ([1] UCLouvain, [2] Clin. Univ. St. Luc, UCLouvain)
Perceiving faces using auditory substitution of vision activates the fusiform face area.

Posters

1. R. YANG[1], T. WALTHER[2], F. GEMBARDT[2], I. SMOLDERS[1], P. VANDERHEYDEN[1], S. CHAI[3], A.G. DUPONT[1] ([1] VUBrussel, [2] Univ.Hull UK, [3] Univ. Melbourne Australia)
AT1a receptor-mediated renal vasoconstrictor and pressor responses to angiotensin IV and angiotensin II in mice.

2. A. SCHALLIER[1], A. MASSIE[1], E. LOYENS[1], D. MOECHARS[2], W. DRINKENBURG[2], Y. MICHOTTE[1], I. SMOLDERS[1] ([1]VUBrussel, [2]Johnson & Johnson Pharm. Res. & Development Beerse)
vGLUT2 heterozygous mice show more susceptibility to clonic seizures induced by pentylenetetrazol.

3. N. AOURZ, D. DE BUNDEL, J. PORTELLI, R. CLINCKERS, Y. MICHOTTE, I. SMOLDERS (VUBrussel)
SSt4 receptor-mediated anticonvulsant actions in rats are abolished by selective SS2 or SSt3 receptor antagonism.

4. W. VERMEULEN, J.G. DE MAN, N.E. RUYSSERS, H.U. DE SCHEPPER, R.M. VAN DEN BOSSCHE, P.A. PELCKMANS, B.Y. DE WINTER (UAntwerpen)
Optimalisation of the time course of TNBS colitis in the rat: a model for postinflammatory dysfunctions.

5. S. STEURBAUT, L. LEEMANS, E. DE BAERE, T. LEYSEN, T. METS, A.G. DUPONT (VUBrussel)
Medication history verification of geriatric inpatients by clinical pharmacists.

6. P. DE COCK, P. DECLERCQ, M. DE VRIENDT, A. DE JAEGER, A. SOMERS, H. ROBAYS (UGent)
Direct observation approach for detecting medication administration errors in a Belgian paediatric medium-care unit.

7. L. LEEMANS [1], S. STEURBAUT, M. LEYS[1], M. PEETERS[1], J. SAEVELS[2], S. SARRE[1], C. VANDERHEYDEN[1], A. VERRYDT[3], L. VEROEVEREN[3], A.G. DUPONT[1] ([1]VUBrussel, [2]Centrum Wetenschapp. Ontwikkeling voor Apothekers, [3]Christelijke Mutualiteiten) (in cooperation with Focus Farmaceutische Zorg vzw)
Assessment of communication and drug related problems by community pharmacists after hospital discharge.

8. N. POELVOORDE, H. VERSTRAELEN, R. VERHELST, B. SAERENS, E. DE BACKER, G. LOPES DOS SANTOS SANTIAGO, C. VERVAET, M. VANEECKHOUTTE, F. DE BOECK, L. VAN BORTEL, M. TEMMERMAN, J-P. REMON (UGent)
In vivo evaluation of the vaginal distribution and retention of a multi-particulate pellet formulation.

9. J. SADONES, E. JOOSENS, F. BOUTTENS, L. VERBEKE, J.-F. BAURAIN, L. D'HONDT, T. STRAUVEN, C. CHASKIS, P. IN'T VELD, A. MICHOTTE, J. DE GREVE, B. NEYNS (VUBrussel)
Stratified phase II trial of Cetuximab in patients with recurrent high-grade glioma.

10. T. CHRISTIAENS, G. DE LOOF, J.M. MALOTEAUX (BCFI Brussels and Gent)
The Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP): past, present and future.

11. N. LABRANCHE, G. BERKENBOOM, J. FONTAINE, S. POCHET (ULBruxelles).
Effects of sidestream cigarette smoke extract and homocysteine on vascular endothelial function.

12. I. CUEVAS, P. PLAZA, P. ROMBAUX, J. DELBEKE, O. COLLIGNON, A.G. DE VOLDER, L. RENIER (UCLouvain)
Olfactory function in early blind humans: psychophysical testing and cerebral cartography.

13. L.A. RENIER[1,2], I. ANUROVA[1,3], A.G. DE VOLDER[2], S. CARLSON[3], J.P. RAUSCHECKER[1]([1]Georgetown Univ. USA, [2]UCLouvain, [3]Univ. Helsinki Finland)
Spatial and non-spatial processing of sounds and vibro-tactile stimuli in the occipital cortex of early blind humans.

14. N. MARKADIEU, R. CRUTZEN, A. BOOM, C. ERNEUX, R. BEAUWENS (ULBruxelles)
Insulin and aldosterone increase sodium transport across A6 cell monolayers by activating hydrogen peroxide production.

15. N. BAEYENS, S. HORMAN, N. MOREL (UCLouvain)
Different activation of ERM proteins by PKC and Rho kinase in vascular smooth muscle.

16. L. MOLLET[1], R. CLINCKERS[2,] R. RAEDT[1], A. MEURS[1], T. WYCKHUYS[1], A. VAN DYCKE[1], R. EL TAHRY[1], K. VONCK[1], W. WADMAN[3], Y. MICHOTTE[2], I. SMOLDERS[2], P. BOON[1] ([1]UGent, [2]VUBrussel & [3]Univ. Amsterdam NL.)
Anti-epileptic effects of Vagus Nerve Stimulation in the focal pilocarpine model.

17. I. DAUWE[1], R. RAEDT[1], A. VAN DYCKE[1], A. MEURS[1], T. WYCKHUYS[1], R. EL TAHRY[1], K. VONCK[1], W. WADMAN[2], P. BOON[1] ([1] UGent & [2] Univ. Amsterdam NL.)
Local infusion of neuropeptide Y has anti-epileptic effects in fully kindled rats.

18. B. VAN NIEUWENHUYSE[1], T. WYCKHUYS[1], R. RAEDT[1], A. MEURS[1], A. VAN DYCKE[1], R. EL TAHRY[1], K. VONCK[1], W. WADMAN[2], P. BOON[1] ([1]UGent & [2]Univ. Amsterdam NL.)
Effect of hippocampal Deep Brain Stimulation on blood perfusion evaluated by µSPECT.

19. A. VAN DYCKE[1], R. RAEDT[1], D. BOISON[2], A. VERSTRAETE[3], A. MEURS[1], T. WYCKHUYS[1], R. EL TAHRY K. VONCK[1], , W. WADMAN[3], P. BOON[1] ([1,3]UGent, [2]RS Dow Labs Portland USA, & [4]Univ. Amsterdam NL.)
Adenosine secretion by neural stem cells isolated from $ADK^{-/-}$ mice.

A B S T R A C T S

O-01

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ (PPARγ) ACTIVATION ALLEVIATES POSTOPERATIVE ILEUS BY INHIBITION OF EGR-1 EXPRESSION AND ITS DOWNSTREAM TARGET GENES

De Backer O.,[1,2] Elinck E.,[1] Lefebvre R.A.[1]
[1]Heymans Institute of Pharmacology, Faculty of Medicine & Health Sciences; [2]Department of Internal Medicine, Ghent University, Belgium

Background & aims: Previous studies have demonstrated that pretreatment of mice with the heme oxygeanse (HO)-1 end product CO markedly reduces the development of postoperative ileus (POI). Recently, it was reported that CO exerts its anti-inflammatory effects through the induction of PPARγ. This led us to specifically investigate the role of PPARγ in the pathogenesis of POI. *Methods***:** Intestinal tissue was analyzed for gene expression, transcriptional activity, inflammatory parameters/enzyme activity, leukocyte infiltration and oxidative stress levels. Intestinal contractility and transit were evaluated by video-fluorescence imaging. *Results***:** Surgical manipulation induced a rapid phosphorylation and subsequent degradation of PPARγ within both intestinal layers of the colon. Accompanying these modifications, there was a decrease in PPARγ DNA-binding activity which was significantly restored by the PPARγ agonist rosiglitazone. The functional severity of POI was significantly ameliorated in mice pretreated with rosiglitazone; this was associated with a down-regulation of inflammatory parameters, iNOS/COX-2 enzyme activity as well as a decrease in leukocyte recruitment into the intestinal muscularis of both colon and jejunum. These anti-inflammatory effects were preceded by a PPARγ-dependent inhibition of surgically-induced Egr-1 induction. Although recent studies reported that PPARγ activation can lead to up-regulation of HO-1 expression, rosiglitazone treatment partially prevented the surgically-induced HO-1 induction in our study. *Conclusions:* These data demonstrate that PPARγ occupies a key role in the pathogenesis of POI and that rosiglitazone prevents POI by suppression of the muscularis inflammatory cascade through a PPARγ-dependent down-regulation of Egr-1.

O-02

FUNCTIONAL STUDY ON THE ROLE OF TACHYKININS IN COLONIC PERISTALTIC ACTIVITY IN MICE

Deiteren A.L.[1], De Winter B.Y.[1], Zizzo M.G.[2], Pelckmans P.A.[1], De Man J.G.[1]
[1]Lab. Exp. Medicine & Pediatrics, Div. Gastroenterology, University of Antwerp, Antwerp, Belgium and [2]Dipartimento di Biologia Cellulare e dello Sviluppo, Lab. di Fisiologia Generale, Università di Palermo, Italy.

Because the role of tachykinin receptors in colonic peristalsis remains incompletely understood, we studied the effect of tachykinin receptor antagonists on mouse colonic peristaltic activity. Peristaltic activity was assessed by quantifying the amplitude and interval of distension-induced pressure waves in proximal and distal colon segments of mice using a modified Trendelenburg set-up. We studied the effect of the NK_1, NK_2 and NK_3 tachykinin receptor antagonists RP67580 (2 µM), nepadutant (1 µM) and SR142801 (0.3 µM) respectively. Gradual distension of proximal and distal colon segments induced repetitive rhythmic pressure waves which were blocked by tetrodotoxin (1 µM) and virtually abolished by hexamethonium (0.1 mM) demonstrating their neuronal origin. The NK_1 receptor blocker RP67580 significantly reduced the amplitude of the pressure waves in segments of proximal (5.9±0.7 to 1.8±0.8 cmH_2O, n=7) and distal (4.8±0.6 to 1.5±0.7 cmH_2O, n=6) colon. RP67580 significantly reduced the interval in the proximal (66±7 to 87±6 s, n=5) but not in the distal colon. The NK_2 receptor blocker nepadutant significantly reduced the amplitude (5.2±0.5 to 3.3±0.7 cmH_2O, n=7) and the interval (52±7 to 39±6 s, n=7) in the proximal colon without affecting peristaltic parameters in the distal colon. Blockade of NK_3 receptors by SR142801 did not affect the amplitude or interval of peristaltic waves in the proximal and distal colon. Combined blockade of NK_1, NK_2 plus NK_3 receptors significantly reduced the amplitude in the proximal colon (6.5±0.9 to 1.6±0.8 cmH_2O, n=6) and prolonged the interval (63±5 to 106±22 s, n=6). Our study shows that mouse colonic peristaltic activity has a strong tachykininergic component that is mediated mainly by NK_1 receptors and to a lesser extent by NK_2 receptors. We could not demonstrate a role for NK_3 receptors.

O-03

IN VITRO AND IN VIVO STUDIES ON THE IMPORTANCE OF THE SOLUBLE GUANYLYL CYCLASE ALPHA $_1$ SUBUNIT IN PENILE ERECTION

Decaluwé K[1]., Nimmegeers S[1]., Thoonen R.[2,3], Brouckaert P.[2,3], Van de Voorde J.[1] (UGent)
[1]Department of Pharmacology, Ghent University, Ghent, Belgium, [2]Department for Molecular Biomedical Research, VIB, Ghent, Belgium, [3]Department of Biomedical Biology, Ghent University, Ghent, Belgium

Penile erection is a highly regulated physiologic event in which the NO-cGMP pathway plays a pivotal role. In the corpora cavernosa, NO is synthesized by both neuronal NOS and endothelial NOS. Independent of its source, NO diffuses to the arterial and corporal smooth muscle cells for binding its target sGC. This enzyme is responsible for the catalyzation of GTP to cGMP. After activation of sGC by NO an increase in cGMP occurs which results in a cascade of events eventually leading to smooth muscle relaxation and penile erection. So sGC plays a key role in the mechanism of erection and seems to be an attractive and promising new target for the treatment of erectile dysfunction. In its molecular make-up, sGC is a heterodimer consisting of an α and a β subunit. Of both subunits, two isoforms have been characterised, however only the $sGC\alpha_1\beta_1$ and $sGC\alpha_2\beta_1$ heterodimers are functionally active. In order to elucidate the functional role of the $sGC\alpha_1\beta_1$ heterodimer in the mechanism of erection, experiments were performed in vivo and on isolated corpora cavernosa using $sGC\alpha_1^{-/-}$ mice. For the in vivo study sGC-dependent and –independent vasorelaxing agents were injected intracavernosally and the rise in intracavernosal pressure was recorded in $sGC\alpha_1^{-/-}$ mice and their littermates. For the in vitro study isolated corpora cavernosa tissues from $sGC\alpha_1^{-/-}$ mice and their littermates were mounted in organ baths for isometric tension recording. When a stable contraction was achieved by administration of 5 µmol/L norepinephrine, concentration-dependent curves were obtained for different sGC-dependent and –independent vasorelaxing agents. These studies were conducted on 2 different mice strains (129SvEvS7 and C57BL6/J) to determine potential stain differences. The responses in $sGC\alpha_1^{-/-}$ to administration of SNP (1 - 4 µg/kg or 10^{-9} – 10^{-5} mol) and spermine-NO (10 - 20 µg/kg or 10^{-9} – 10^{-5} mol) and to EFS (1 - 8 Hz, 80V, 20s) or stimulation of the nervus cavernosus (5 - 15 Hz, 8V, 60s) are significantly reduced although not completely abolished, illustrating the importance of the $sGC\alpha_1\beta_1$ heterodimer. However this study also provides evidence that activation of $sGC\alpha_1\beta_1$ is not the sole mechanism responsible for penile erection.

O-04

THE SECRETORY PATHWAY CA^{2+}-ATPASE 1 (SPCA1) IS LOCALIZED IN CHOLESTEROL-RICH DOMAINS OF COLON CARCINOMA CELLS

Baron S., Wuytack F., Raeymaekers L., Vanoevelen J.
Laboratory of Ca^{2+} transport ATPases, Department of Molecular Biology, KULeuven

The membrane of the endoplasmic reticulum (ER) is one of the most fluid of all cellular membranes. Hence, the Sarco/Endoplasmic Reticulum Ca^{2+} ATPases (SERCAs) are well adopted to function in cholesterol-poor highly fluid membranes. Lipid rafts are thought to first assemble in the Golgi. Thus, the membranes of the Golgi complex are more enriched in cholesterol and therefore are more rigid. Lipid rafts have been characterized by their relative insolubility at low temperatures in detergents such as Triton X-100. Also it has been found that detergent-resistant membranes are enriched in sphingomyelin and cholesterol.
In our study, the microdomain localization of the Secretory Pathway Ca^{2+} ATPase 1 (SPCA1) was investigated by Triton X-100 detergent extraction of HT29 cells. Fractions from extracts were analyzed for total cholesterol content and for SPCA1 and marker proteins by Western blotting. Similarly to cholesterol and the raft-resident protein flotillin-2, SPCA1 was found mainly in detergent-resistant fractions, while SERCA3 was detergent soluble. In addition, the time course of solubilization by Triton X-100 was investigated in living COS-1 cells transfected with glycosyl-phosphatidylinositol-anchored (GPI)-CFP, vesicular stomatitis virus G (VSVG)-YFP, SERCA2b-GFP or SPCA1d-GFP. As already reported[1], GPI-CFP was highly resistant to Triton X-100 solubilization, while VSVG-YFP non-raft protein was gradually solubilized. SERCA2b-GFP ER-resident protein also showed a gradual decrease of GFP fluorescence, up to 70% in 3 min. In contrast, SPCA1d-GFP fluorescence decreased by only 10%.
From these results we conclude that SPCA1 is localized in cholesterol-rich and detergent-resistant domains of colon carcinoma cells.

[1]Garner *et al.*, (2008) Biophys. J. 94:1326-1340.

O-05

PHARMACOKINETIC STUDY OF OMEPRAZOLE MULTI-UNIT PELLET SYSTEM (LOSEC MUPS®) VERSUS EXTEMPORANEOUS BICARBONATE FORMULATION IN PATIENTS WITH CEREBRAL PALSY AND MENTAL RETARDATION

De Smet J.[1], Boussery K.[1], Van Winckel M.[2], De Cock P.[3], De Paepe P.[4], Remon J.P.[1], Van Bocxlaer J.[1]

[1]Ghent University, Pharmaceutical Sciences, [2]Ghent University Hospital, Paediatric Gastro-enterology Dpt., [3]Ghent University Hospital, Pharmacy Dpt., [4]Ghent University, Heymans Institute of Pharmacology.

Background: In patients with tube feeding, omeprazole is often used off-label as an extemporaneous formulation (suspension in 8.4 % bicarbonate). Few pharmacokinetic data on the use of this suspension are available. *Objective:* To compare the pharmacokinetics of omeprazole suspension with omeprazole MUPS. *Method*: The study population consisted of 10 patients (7 female, age 7 - 26 yrs) with cerebral palsy and mental retardation, treated with omeprazole because of oesophagitis grade B-D. In a randomized cross-over design, standard omeprazole dose (20 or 40 mg) was administered for a 14-day period as Losec MUPS® followed by a 14-day period as a 8.4 % bicarbonate suspension or vice versa. All doses were administered through a gastrostomy tube in accordance to local guidelines. On day 15 and day 29 a series of venous blood samples were drawn pre- and postdose. Omeprazole plasma levels were determined by hydrophilic interaction chromatography with tandem mass spectrometry. *Results*: In all patients, time till peak plasma level (Tmax) was shorter with suspension (range 0.5-1h) versus MUPS (range 1-6h). In 7/10 patients, area under the plasma concentration time curve (AUC) and peak plasma levels (Cmax) were at least doubled after administration of suspension (AUC 376 – 34,653 µg.h.L^{-1}; Cmax 570-5,619 µg/L) compared to MUPS (AUC 51 – 9,036 µg.h.L^{-1}; Cmax 18 – 2,110 µg/L). In 3/10 patients however, administration of MUPS resulted in higher AUC and Cmax compared to suspension. *Conclusion*: Even though interindividual variability in omeprazole pharmacokinetics is substantial, the suspension in 8.4 % bicarbonate shows a consistently shorter Tmax compared to MUPS, with bioavailability being better for suspension in 7/10 patients.

O-06

AN IRREVERSIBLE DUAL INHIBITOR OF EGFR AND HER2 IN BIOMARKED ADENO-CARCINOMA OF THE LUNG

De Greve J., Teugels E., Galdermans D., De Mey J., In ‘tveld P., Geers C., Decoster I., Schallier D., Taton M., Shahidi M. (VUBrussel)

Abstract not available

O-07

INFLUENCE OF TOCOLYTICS ON CENTRAL AND PERIPHERAL HEMODYNAMICS

Fabry I.[1,2], De Paepe P.[1], Van Bortel L.[1,2]
[1]Heymans Institute of Pharmacology, Ghent University and [2]Drug Research Unit Ghent, Ghent University Hospital, B-9000 Ghent, Belgium.

Objective: Atosiban and ritodrine are frequently used tocolytics with only few studies investigating their hemodynamic effects. We therefore aimed to study both their central and peripheral hemodynamics using noninvasive methods.
Methods: Twenty healthy female volunteers (19-41 yrs) were given atosiban (300 µg/min over 2 h) and placebo intravenously (IV) in a random crossover design. Eight of them also received ritodrine IV in escalating doses up to 400µg/min over 2 h. The hemodynamics were noninvasively investigated at fixed time points using blood pressure (BP), applanation tonometry for augmentation pressure on the common carotid artery and echocardiography for cardiac output (CO). Statistical analysis was done using Friedman and Wilcoxon test setting value of significance at 0.05.
Results:

Parameters	***Ritodrine (n=8)***	***Atosiban(n=20)***	***Placebo (n=20)***	p-value[$]
SBP(mmHg)	114±13[*#]	105±8	105±6	<0.001
DBP(mmHg)	58±9[*#]	70±7	68±5	<0.001
HR (bpm)	103±14[*#]	59±9	57±8	<0.001
MAP(mmHg)	76±10[*#]	84±8	83±6	<0.001
PP (mmHg)	56±7[*#]	37±5	35±5	<0.001
CO (l/min)	5.5±1.5[*#]	3.0±1.0	3.0±0.9	0.002
AGPP@HR75 (mmHg)	-8.67±12.30	2.29 ±17.35	4.38±13.67	0.368

SBP (systolic BP), DBP (diastolic BP), HR (heart rate), MAP (mean arterial pressure), PP (pulse pressure), AGPP@HR75 (augmentation pressure corrected for HR at 75bpm).
[$] Friedman-test; [*] significant vs. atosiban, [#] significant vs. placebo.

Conclusion: The data show that ritodrine unlike atosiban has important central and peripheral hemodynamic effects reflected by cardiac stimulation (increasing HR and CO) and a decrease in peripheral resistance (decrease in MAP and augmentation pressure).

O-08

IS PROPOFOL THE PERFECT HYPNOTIC AGENT FOR PROCEDURAL SEDATION IN NEONATES?

Allegaert K.[1], Verbesselt R.[2], Naulaers G.[1], De Hoon J.[2] (KULeuven)
[1]Neonatal Intensive Care Unit and [2]Center for Clinical Pharmacology, University Hospitals, Leuven, 3000 Belgium.

Introduction: Following the landmark observations on the relevance of adequate analgesia and sedation in neonates, neonatologists are in search for short acting agents for procedural sedation. Propofol (2,6 di-isopropylphenol) is considered to be a short acting anaesthetic that is both rapid in onset and short in duration after cessation, but data on pharmacokinetics and metabolism in neonates were absent.
Methods: In 3 consecutive studies, data on propofol pharmacokinetics and metabolism were collected in neonates after single intravenous (3 mg/kg) bolus administration (ref 1-3).
Results: Median propofol clearance (19.6 mL kg^{-1} min^{-1}) is significantly lower and interindividual variability (range 3.7-78 mL kg^{-1} min^{-1}) in propofol clearance in neonates is extensive. Simultaneous introduction of postmenstrual and postnatal age as covariates resulted in a reduction of this interindividual clearance from 322 to 84 %. Finally, differences in clearance are due to limited capacity for glucuronidation in neonates, only in part compensated by hydroxylation.
Conclusions: Clinicians should remain careful with propofol in neonates because of the reduced clearance and extensive interindividual variability. We strongly dissuade the use of continuous or repeated intermittent administration of propofol in the first weeks of life and suggest to study the pharmacodynamics of single bolus administration of propofol in neonates.

Ref: Paediatr Anaesth 2007;17:1028-34 - Br J Anaesth 2007;99:864-70 –
Br J Anaesth 2008;101:827-831

O-09

BENEFIT RISK ASSESSMENT OF OLDER PRODUCTS

De Backer T., Vander Stichele R., Van Bortel L.
Heymans Institute of Pharmacology Ghent University

Background: Benefit risk assessment should be ongoing during the life-cycle of a pharmaceutical agent. New products are subjected to rigorous registration laws and rules, which attempt to assure the availability and validity of evidence. For older products, bias in benefit risk assessment is more likely, as a number of safeguards were not yet into place when these products were registered.
Objectives: To clarify the issue of bias in benefit risk assessment of older products with an example: buflomedil in intermittent claudication
Methods: For efficacy: a Cochrane systematic review; for safety: a comparison of the number of reports of serious adverse events and fatalities published in the literature and reported in postmarketing surveillance databases.
Results: For efficacy, the slim basis of evidence for benefit of buflomedil is undermined by documented publication bias. For safety, bias in reporting to international safety databases is illustrated by the discrepancy between the number of drug-related fatality cases published in the literature (20) and deaths from all causes in the WHO database (17), in the database of the company (11).
Conclusions: In older products, efficacy cannot be evaluated without a thorough search for publication bias. For safety, case reporting of drug-related serious events and deaths in the literature remains a necessary instrument for risk appraisal of older medicines, despite the existence of postmarketing safety databases. The enforcement of efficient communication between health care workers, drug companies, national safety committees and the WHO is necessary to assure the validity of postmarketing surveillance reporting systems. Drugs considered obsolete because of unfavourable benefit risk assessment should not be allowed to stay on the market.

O-10

MEDICAL PRESCRIBING FOR INSTITUTIONALIZED DEMENTED PATIENTS

Vander Stichele, RH.[1], Elseviers M.[2]
[1]Heymans Institute of Pharmacology, Ghent University [2]Department of Nursing Sciences, Antwerp University, Ghent, B-9000 Belgium.

Background: The PHEBE project (Prescribing in Homes for the Elderly in Belgium) investigated the quality of prescribing in nursing homes (NHs). We focused on the medical treatment of demented residents.
Objectives: To investigate the quality of medical prescribing in demented residents (D) of NHs compared to cognitive intact elderly (non-D).
Methods: In this cross-sectional observational study, NHs (> 30 beds, long term intermediate care) were randomly selected in 3 Belgian provinces. In each NH, 40 residents were randomly selected. Key administrative and clinical data (incl. dementia score (grade 1 to 5) based on disorientation in time and place) was collected for each resident. A reprint of the medication chart was sent to the treating physician asking to check and to complete with clinical and care problems (incl. diagnosis of dementia). Patients in palliative care were excluded for this analysis. Descriptive statistical methods were used, the significance level was set at $p<.05$.
Results: Dementia was diagnosed in 46% out of 1730 included residents. Compared to non-D, D-residents had the same age (mean 85) with more females (81% versus 75%). Clinical problems noticed by the GP gradually decreased from a mean of 2.9 (95%CI 2.7-3.0) in grade 1 to 1.6 (95%CI 1.3-1.9) in grade 5. Compared to non-D, D-residents had significantly less clinical diagnoses of hypertension, vascular disease, heart failure, COPD, gout and peptic ulcer. Additionally, in D-residents, a significant decrease was observed in the reported diagnosis of chronic pain and insomnia while decubitus, fall risk and incontinence increased. Accordingly, prescriptions for chronic medication gradually decreased from a mean of 7.7 (95%CI 7.4-8.0) to 5.1 (95%CI 4.5-5.8). In D-residents, significantly ($p<.001$) less cardiovascular medication, analgesic and NSAIDs were prescribed. Medication of the nervous system was comparable (90%) in both groups with an increase for antidepressants (from 43% in non-D to 49% in D) and a decrease in benzodiazepines (from 59% in non-D to 43% in D). Total public expenditures for medication were identical in both groups. However, out of pocket expenditures decreased in D-residents, both for reimbursed and non-reimbursed medication.
Conclusions: Medication use decreased with increasing grade of dementia in institutionalized elderly. Question arises if this observation points to ‘justified therapeutic abandonment‘ or to the under-treatment of demented residents?

O-11

SYSTEMIC INJECTION OF A SK BLOCKER INCREASES BURSTING OF MIDBRAIN DOPAMINE NEURONS IN AWAKE RATS

Koulchitsky S.[1], Waroux O.[1], Liégeois J.-F.[2] and Seutin V.[1]
[1] Laboratory of Pharmacology and GIGA Neurosciences, and [2] Laboratory of Medicinal Chemistry and Drug Research Center, ULg, B-4000 Liège, Belgium

Small conductance Ca^{2+}-activated K^+ channels (SK channels) are known to underlie the medium duration afterhyperpolarization in various types of CNS neurons. Previous experiments demonstrated that local SK channel blockade increases bursting in dopaminergic and serotonergic, but not noradrenergic neurons *in vivo* in anaesthetized rats (Waroux et al., 2005; Rouchet et al., 2008). The present study was conducted in awake rats using telemetric recordings. Wistar rats were implanted with microelectrode arrays made of 8 platinum electrodes (Alpha Omega®) in the ventral t egmental area. Neural activity was recorded during four sessions: one baseline session, without any experimental manipulation, and three sessions in which the rats (n = 5) received intraperitoneal injections of saline, the D2 agonist quinpirole (100 µg/kg) or the novel tertiary SK blocker AG525E1 (10 mg/kg) (Graulich et al., 2008). In total, 14 neurons were recorded. Injection of saline did not lead to any significant change in firing rate or pattern in any of the recorded neurons. Seven neurons had a long-lasting action potential. Their firing was completely inhibited by quinpirole within 5-15 min after its injection, which suggests that these neurons were dopaminergic. Within 20 min after the injection of AG525E1, these neurons underwent an increase in firing rate from 2.5 ± 1.3 to 5.6 ± 1.5 Hz, and an increase in the % of spikes in bursts from 6 ± 1 to 31 ± 6%. The effects of AG525E1 disappeared 40-45 min after the injection. Neither quinpirole nor AG525E1 had any significant effect in the other 7 neurons. These results suggest that SK channel blockade could enhance dopamine transmission. Therefore, the development of drugs crossing the blood-brain barrier and reversibly affecting SK channels may be a promising approach for treating CNS diseases.

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O-12

CHARACTERIZATION OF A SK-MEDIATED MEDIUM DURATION AFTER HYPER-POLARIZATION IN DORSAL RAPHE NEURONS

Alix P., Seutin V.
GIGA Neurosciences and Laboratory of Pharmacology, ULg, B-4000 Liège, Belgium.

Most Dorsal Raphe neurons display two characteristics: a long duration (2 ms) action potential due to the presence of a shoulder on its falling phase and a prominent afterhyperpolarization (AHP) following the action potential (Beck et al., 2003; Scuvée-Moreau et al., 2004). Recent in vivo experiments suggest that SK channel blockade increases bursting in serotonergic neurons in this area (Rouchet et al., 2008). The purpose of this study was therefore to characterize the currents responsible for the AHP in these neurons. Using whole-cell recordings of infra-red visualised neurons in acute slices, we elicited and recorded AHP currents under voltage-clamp conditions with repetitive short (20 ms) unclamped depolarizations (holding and recording potential, -60 mV; steps to -10 to +100 mV; (Wolfart and Roeper, 2002)). After pulses to +100 mV, a putative AHP current appeared as an outward current peaking at about 100 ms after the depolarizing pulse. This current had kinetics comparable to those of I_{AHP} (Stocker, 2004). A supra-maximal concentration of the SK channel blockers apamin (300 nM) and (-)-bicuculline methiodide (BMI; 100 µM) blocked these outward currents. Block by BMI was reversible and mimicked by an ulterior application of apamin. Block by both agents uncovered an inward current which was sensitive to cobalt (1 mM), as previously observed in hippocampal neurons by Stocker et al. (1999). Moreover, application of cobalt blocked both the inward and outward currents generated in the absence of BMI and apamin. Block of I_{AHP} by apamin, BMI and cobalt suggests that I_{AHP} of Dorsal Raphe neurons is induced by SK channel activation following the opening of voltage-dependant calcium channels.

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O-13

INVESTIGATIONS INTO THE ROLE OF SOMATOSTATIN IN THE ANTICONVULSIVE EFFECTS OF INSULIN-REGULATED AMINOPEPTIDASE INHIBITORS

De Bundel D.[1], Loyens E.[1], Kiagadaki F.[2], Aourz N.[1], Stragier B.[1], Michotte Y.[1], Thermos K.[2], Smolders I.[1].

[1] Research Group Experimental Pharmacology, Department of Pharmaceutical Chemistry and Drug Analysis, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

[2] Laboratory of Pharmacology, Department of Basic Sciences, Faculty of Medicine, University of Crete, 71110, Heraklion, Greece.

The neuropeptide somatostatin is an important regulator of hippocampal excitability and several lines of evidence implicate its involvement in temporal lobe epilepsy. In the present study we investigate the anticonvulsive effects of two distinct peptide inhibitors of insulin-regulated aminopeptidase (IRAP), Ang IV and LVV-H7, in the focal pilocarpine model for limbic seizures. Both IRAP inhibitors were administered into the hippocampus of freely moving rats using the microdialysis technique. The anticonvulsive effect of both Ang IV and LVV-H7 was abolished by pretreatment with the somatostatin sst2 receptor antagonist cyanamid 154806. Somatostatin similarly had a potent anticonvulsive effect through activation of the sst2 receptor subtype. Given that somatostatin has been characterized as a substrate of IRAP we hypothesized that IRAP inhibitors may exert their effects through inhibition of somatostatin degradation. We investigated the effects of IRAP inhibitors on extracellular hippocampal somatostatin levels before and after potassium-evoked somatostatin release. We found that both IRAP inhibitors did not affect extracellular hippocampal somatostatin but suppressed potassium-evoked somatostatin release. This suggests that the extracellular concentration of somatostatin is tightly controlled in the hippocampus. Indeed, we found that the sst1 receptor antagonist SRA880 increases extracellular hippocampal somatostatin levels. This demonstrates that the sst1 receptor is an autoreceptor in the hippocampus. We therefore propose that a potential effect of IRAP inhibitors on extracellular hippocampal somatostatin may be counteracted by further activation of the sst1 receptor. The observation that IRAP inhibitors suppressed potassium-evoked somatostatin release further supports the notion of an increased “somatostatin tonus”. Further clarification of the mechanism of action of IRAP inhibitors may identify a novel anticonvulsive treatment strategy.

O-14

PERCEIVING FACES USING AUDITORY SUBSTITUTION OF VISION ACTIVATES THE FUSIFORM FACE AREA

Plaza P.[1], Cuevas I.[1], Collignon O.[1], Grandin C.[2], De Volder A.G.[1], Renier L.[1]
[1] Neural Rehabilitation Engineering Laboratory, Université Catholique de Louvain
[2] Department of Radiology, Functional magnetic resonance imaging section Université catholique de Louvain, Cliniques Universitaires Saint-Luc

Previous neuroimaging studies identified the fusiform face area (FFA) in the ventral visual cortex as a region specialized in the visual processing of faces. Here, we tested whether the FFA was recruited during face perception using a prosthesis substituting vision by audition (PSVA). Using functional magnetic resonance imaging in blindfolded volunteers, we compared the brain activation patterns during the recognition of faces, man-made objects and meaningless images with the PSVA. Face-related activation foci were found in occipito-temporal brain areas, including the fusiform gyrus in and around the FFA. The object recognition task activated a larger occipito-temporal network including the same coordinates as face, whereas meaningless images did not recruit any visual brain area. We conclude that perception provided by sensory substitution involves the same brain structures as direct vision, indicating a specific functional organization of these brain areas to allow perception of faces or man-made objects independently of the sensory modality.

P-01

AT_{1A} RECEPTOR-MEDIATED RENAL VASOCONSTRICTOR AND PRESSOR RESPONSES TO ANGIOTENSIN IV AND ANGIOTENSIN II IN MICE

Yang Y.[1], Walther T.[2], Gembardt F.[2], Smolders I.[1], Vanderheyden P.[1], Chai S.[3], Dupont A.G.[1].
[1]Vrije Universiteit Brussel, Brussels, 1090 Belgium, [2]University of Hull, UK, [3]University of Melbourne, Victoria 3010 Australia

Angiotensin IV (Ang IV) has been reported to induce renal vasodilation in rats via AT_4 receptors in some studies but renal vasoconstriction mediated by activation of AT_1 receptors in other studies. AT_4 receptor was characterized as the insulin-regulated aminopeptidase (IRAP), a membrane anchored zinc-dependent metalloproteinase. We investigated the effect of Ang IV and angiotensin II (Ang II) on mean arterial pressure (MAP) and renal cortical blood flow (CBF) in wild type (WT), AT_{1a}, AT_{1b}, AT_2 receptor and IRAP knockout mice. MAP was recorded via a femoral catheter and CBF was measured using a laser Doppler probe; cortical vascular resistance (CVR) was calculated as MAP divided by CBF. Baseline values of MAP, CBF and CVR in WT mice were 71.8±3.9 mmHg, 78.8±6.7 ml/min and 1.0±0.1 mmHg.min/ml, respectively. Baseline MAP, CBF and CVR were significantly lower in AT_{1a} (-/) as compared to WT animals. AT_2 (-/-) mice had a significantly higher baseline MAP, but similar CBF and CVR. Ang IV and Ang II dose–dependently increased MAP and CVR, and reduced CBF in WT mice; these responses were antagonized by AT_1 receptor blockade with candesartan. The pressor and renal vasoconstrictor responses to both peptides were almost completely abolished in AT_{1a} (-/-), but tended to be enhanced in AT_2 (-/-) mice. The responses in AT_{1b} (-/-) and IRAP (-/-) mice did not differ from those in WT mice. AT4-16 (100 nmol/kg) did not induce any effect in all types of mice. The results demonstrate that Ang IV and Ang II mediate pressor responses and reduce renal blood flow in mice through stimulation of AT_{1a} receptors, and suggest that the presence of AT_2 receptors may counteract these responses to some extent. The results do not provide evidence for a putative IRAP mediated vasodilator effect.

P-02

VGLUT2 HETEROZYGOUS MICE SHOW MORE SUSCEPTIBILITY TO CLONIC SEIZURES INDUCED BY PENTYLENETETRAZOL

Schallier A.[1], Massie A.[1], Loyens E.[1], Moechars D.[2], Drinkenburg W.[2], Michotte Y.[1], Smolders I.[1]

[1]Research Group Experimental Pharmacology, Department of Pharmaceutical Chemistry, Drug Analysis and Drug Information, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium

[2]Johnson & Johnson Pharmaceutical Research and Development, A Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

Glutamate, the most abundant excitatory neurotransmitter in the central nervous system, is well known to be implicated in epileptic seizures. Therefore, impairments in glutamate transport could have an involvement in the mechanism of epileptogenesis. The uptake of glutamate into synaptic vesicles is mediated by vesicular glutamate transporters (vGLUTs). There are three known vGLUT isoforms, vGLUT1-3. In this study, we are particularly interested in the vGLUT2 isoform. We investigated the possible role of vGLUT2 in pentylenetetrazol (PTZ)-induced seizure generation. Seizure threshold of PTZ was compared in vGLUT2 heterozygous knock out (HET) and wild type (WT) mice. In comparison with their WT littermates a lower dose of PTZ was needed in the vGLUT2 HET mice until the onset of the first myoclonic jerk. The threshold for PTZ-induced clonic seizure activity was also lower in the vGLUT2 HET mice. These results indicate, for the first time, that vGLUT2 is likely involved in the epileptogenesis of generalized seizures.

P-03

SST4 RECEPTOR-MEDIATED ANTICONVULSANT ACTIONS IN RATS ARE ABOLISHED BY SELECTIVE SST2 OR SST3 RECEPTOR ANTAGONISM

Aourz N., De Bundel D., Portelli J., Clinckers R., Michotte Y., Smolders I.
Research Group Experimental Pharmacology, Department of Pharmaceutical Chemistry, Drug Analysis and Drug Information, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

Anticonvulsant actions have already widely been proven for somatostatin-14 (SST-14). The contribution of the (SST1-SST5) receptors in these anticonvulsant actions is poorly understood and many interspecies differences have been shown. Recent studies pointed to the involvement of the SST4 receptors in regulating hippocampal excitability, although both SST4-mediated pro-and anticonvulsant effects have been demonstrated *(1,2)*. To investigate the importance of this receptor in rats, we used L-803,087, a selective SST4 receptor agonist. In vivo microdialysis in male albino Wistar rats was used for intrahippocampal drug administration. Seizures were evoked by intrahippocampal pilocarpine perfusion (10mM, 40 min) and seizure severity was assessed using a behavioural scoring system. We showed that intrahippocampal administration of L-803,087 (100nM) was able to prevent pilocarpine convulsions. Coperfusion experiments of this agonist with cyanamid 154806 (CYN), a selective SST2 receptor antagonist, or SST3-ODN8, a selective SST3 receptor antagonist clearly reversed the anticonvulsant actions of L-803,087. CYN or SST3-ODN8 perfusion alone did not significantly alter the pilocarpine induced seizures. These observations point to an important involvement of the SST2 or SST3 receptor in mediating the anticonvulsant actions of the SST4 receptor. A functional coupling between SST2 and SST4 receptors was also previously shown in mice, although in that study, SST4 showed proconvulsant properties *(2).* These findings suggest a major role for the SST4 receptor in mediating the anticonvulsant actions of SST-14 in rats. Once again the importance of interspecies differences within this research domain is emphasized.

References: (1) Qiu et al. (2008) J Neurosc 28:3567, (2) Moneta et al. (2002) J Neurosc 16:843

P-04

OPTIMALISATION OF THE TIME COURSE OF TNBS COLITIS IN THE RAT: A MODEL FOR POSTINFLAMMATORY DYSFUNCTIONS

Vermeulen W.*, De Man J.G.*, Ruyssers N.E.*, De Schepper H.U.*, Van den Bossche R.M.†, Pelckmans P.A.*, De Winter B.Y.*

*Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology, Faculty of Medicine and †Laboratory of Pharmacology, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium.

In the gastrointestinal wall, inflammation can induce long-lasting alterations in visceral sensation and bowel motility even when overt signs of acute inflammation have subsided. This is clinically documented in patients suffering from chronic inflammatory bowel diseases in remission and patients suffering from postinflammatory irritable bowel syndrome. Although the modulating role of intestinal inflammation in these disorders is acknowledged, validated animal models for the investigation of the underlying pathophysiological mechanisms are scarce.

The aim of this study was to optimise a postinflammatory animal model to study the pathophysiological mechanisms involved in the occurrence of motility and sensitivity disorders following an episode of acute colitis.

Colitis was chemically induced in female Wistar rats (180–200 g; n at least 10 per group) by intracolonic instillation of 7.5 mg trinitrobenzene sulphonic acid (TNBS) in 30% ethanol. Control rats received a saline instillation. To explore the TNBS-induced colonic inflammatory response in a time-dependent manner, rats were sacrificed respectively 3 days, 1 week, 2 and 4 weeks after TNBS administration. Inflammation was assessed by a macroscopic (0–10) and microscopic (0–6) score next to a myeloperoxidase (MPO) assay.

Intracolonic instillation of TNBS induced an acute and mild colonic inflammation within 3 days, which was characterized macroscopically by hyperaemia, oedema, ulceration and limited necrosis with a median macroscopic score of 4 (2-6). Histological examination of the inflamed region showed thickening and oedema of the submucosa, localized ulceration and infiltration of inflammatory cells resulting in a median microscopic score of 3 (1-4). Colonic MPO levels increased from 0.3 ± 0.1 U/g in controls to 10.5 ± 3.2 U/g 3 days after TNBS instillation ($p < 0.05$). One week after TNBS, the median macroscopic damage score was 0 (0-2) and the median histological score was 0 (0-2). However, the MPO level was still elevated to 10.3 ± 4.6 U/g compared to 1.1 ± 0.3 U/g in controls ($p < 0.05$) indicating that an inflammatory infiltrate was still present. Two weeks after TNBS instillation, inflammation subsided completely macroscopically, whereas some rats still showed minor inflammatory changes on histological sections (median damage score of 0 (0-1)). Colonic MPO content remained elevated to 4.5 ± 2.7 U/g compared to 1.3 ± 0.4 U/g in controls. Four weeks after colitis induction, no significant differences between saline- and TNBS-treated animals remained, illustrating complete resolution of the TNBS-induced inflammation.

These data demonstrate that a single dose of 7,5 mg TNBS dissolved in 30 % ethanol resulted into a colitis which is transient and self-limiting within 4 weeks. It should be noted that optimising and evaluating postinflammatory conditions is the first step in the development of an animal model that mimics pathophysiological symptoms as seen in postinflammatory bowel diseases.

P-05

MEDICATION HISTORY VERIFICATION OF GERIATRIC INPATIENTS BY CLINICAL PHARMACISTS

Steurbaut S., Leemans L., De Baere E., Leysen T., Mets T., Dupont A.G.
Seamless Care Research Group, Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel, 1090 Brussel, Belgium

Background and Objective: Accurate medication histories at the time of hospital admission are an important element of medication safety, since errors may have clinically significant consequences particularly in the elderly population. The purpose of the study was to assess the clinical pharmacists' performance in obtaining patients' medication histories and in reconciling these lists with the medical records.
Design: Clinical pharmacists interviewed geriatric patients within 48h after hospital admission to obtain their medication history. In some cases, a caregiver and/or the community pharmacist, or written information provided by the general practitioner were also consulted. The medication histories acquired by the pharmacists were compared with those documented in the medical records by the physicians.
Setting: The study was conducted at a Belgian university hospital's 29 beds geriatric ward.
Main outcome measures: Quantitative and qualitative analysis of omitted medication and other discrepancies such as incorrect drug identification, dose, frequency, time, and form as well as therapeutic duplication.
Results: 152 consecutive patients were interviewed. In 13 additional cases, a patient interview was impossible and no other information was available. The mean number ± SD of preadmission medicines correctly identified by the physicians at the ward was 6,6 ± 3,4 (total of 999 in these 152 patients) compared to 7,8 ± 3,7 (total of 1181) as identified by the clinical pharmacists. Additionally identified drugs consisted of OTC as well as prescription medication. Furthermore, 83 other medication discrepancies were noted. Of these discrepancies, 41% were related to a misidentification, 35% to an incorrect dose, 10% to an incorrect form, 7% to an incorrect frequency, 6% to an incorrect time, and 1% to therapeutic duplication. Overall, the clinical pharmacists identified 265 (22%) medication discrepancies of which 135 (51%) were judged clinically relevant in consensus by a clinical pharmacologist and a senior geriatrician.
Conclusions: Clinical pharmacist-acquired medication histories through interview of geriatric patients and their caregivers enhance the medication reconciliation process. This may help to reduce the number of potentially clinically important medication errors.

P-06

DIRECT OBSERVATION APPROACH FOR DETECTING MEDICATION ADMINISTRATION ERRORS IN A BELGIAN PAEDIATRIC MEDIUM-CARE UNIT

De Cock P.[1], Declercq P.[1], De Vriendt M.[2], de Jaeger A.[2], Somers A.[1], Robays H.[1]
Pharmacy Dpt.[1], Paediatric Intensive Care Dpt.[2], University Hospital, 9000 Ghent, Belgium

Objective: To assess the incidence, nature and severity of medication administration errors in a paediatric medium-care unit, in order to develop methods to improve the quality of medication administration. *Methods:* A one-month period, prospective, observational study was conducted in 45 patients admitted to a 6-bed paediatric medium-care unit of the Ghent University Hospital, Belgium. The undisguised direct observation technique was used to detect medication administration errors. Severity of errors was evaluated by an independent clinical pharmacist according to the National Coordinating Council of Medication Error Reporting (NCC MERP) severity index[1]. A drug administration error was defined as any discrepancy between the physician's order and the administration of the drug to the patient. *Results:* During 180 patient days, a total of 220 administration errors (78.0 %) were detected out of 282 observed administrations and divided into the following subtypes: wrong preparation or administration technique (64.1 %), ignored drug-food interaction (12.7 %), time error (12.3 %), omission error (4.1 %), dosing error (3.6 %), wrong drug or dosage form (1.8 %) and unordered drug (1.4 %). Drugs which most commonly contributed to a medication error were antiinfectives (31.4 %) and antiepileptics (28.1%). The enteral administration route accounted for most errors (54.5 %). All medication errors reached the patient with 213 errors (96.8%) categorized as severity category C (i.e. no patient harm), 3 errors (1.4 %) as category D (i.e. with requirement of monitoring to exclude harm or intervention to preclude harm) and 4 errors (1.8 %) as category E (i.e. temporary harm requiring intervention). *Conclusions:* Despite nurse awareness of the study objectives, medication administration errors frequently occurred on our paediatric medium-care unit. In relation to other studies[2,3] under comparable conditions, a higher rate of wrong preparation and administration technique was observed. Therefore, a preparation-administration standardization, education and double check before administration is recommended, especially for drugs with a narrow therapeutic window. *References:* [1]National Coordinating Council for Medication Error Reporting And Prevention. Medication Error Index available from: http://www.nccmerp.org/ (cited : January 2008); [2]Prot et al. Drug administration errors and their determinants in pediatric in-patients. Int J Qual Health Care 2005;17,381-389; [3]Buckley M.S. et al. Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. Pediatr Crit Care Med 2007;8:145-152.

P-07

ASSESSMENT OF COMMUNICATION AND DRUG RELATED PROBLEMS BY COMMUNITY PHARMACISTS AFTER HOSPITAL DISCHARGE

Leemans L.*, Steurbaut S., Leys M.*, Peeters M.*, Saevels J. †, Sarre S.*, Vanderheyden Ch.*, Verrydt A. ‡ , Veroeveren L. ‡, Dupont A.G.*, In cooperation witch Focus Farmaceutische Zorg, v.z.w.

*:Research Group Seamless Care (liesbeth.leemans@vub.ac.be)
VUB; Laarbeeklaan 103 1090 Brussels Belgium

†: Centrum Wetenschappelijke Ontwikkeling voor Apothekers

‡: Christelijke Mutualiteiten

Objectives: To assess the problems a community pharmacist encounters when a patient is discharged from hospital and the way he solves these problems. The study also investigates which information from the hospital reaches the community pharmacy.

Design: A validated 6-page survey was presented, by community pharmacists, to patients or their family after hospital discharge, between the 1st of December 2007 and the 29th of February 2008. Pharmacists enclosed a copy of the patient's medication history.

Setting: Flemish community pharmacies

Main outcome measures: The survey contained questions on 4 items: patient characteristics – discharge medication – information brought from hospital – drug related problems and pharmacists' interventions. Analyses are done with SPSS 16.0.

Main results: 82 community pharmacists participated. 261 patients were included. Only in 25% of the cases the patient picked up their medication themselves.

After discharge, patients on average got 2 more drugs when they left hospital, compared to the pre-hospital situation. Changes in medication patterns are correlated with the duration of hospital stay (p=0,007).

69% received a medication scheme, but less than half of them brought this scheme along when visiting the pharmacy. The chance to detect a problem enlarged significantly when the scheme was brought to the pharmacy (p=0,033). Only 9% received electronic prescriptions from the hospital and < 3% received a letter of referral meant for their pharmacist.

In 1/3 of the cases the pharmacists noticed one or more problems concerning the prescribed medication. When phoning the hospital, the community pharmacist was only able to reach the treating specialist in less than one third of those cases.

Conclusion: This survey reveals some shortcomings, noticed when a patient is discharged from hospital. The results foster the discussion on the need for a better seamless care and the role clinical and community pharmacists have to play in this care model.

P-08

IN VIVO EVALUATION OF THE VAGINAL DISTRIBUTION AND RETENTION OF A MULTI-PARTICULATE PELLET FORMULATION

Poelvoorde N.[1], De Boeck F.[2], Verstraelen H.[3], Verhelst R.[4], Saerens B.[4], De Backer E.[4], Lopes dos Santos Santiago G.[4], Vervaet C.[1], Vaneeckhoutte M.[4], Van Bortel L.[2,5], Temmerman M.[3], J-P. Remon J.P.[1]

[1]Laboratory of Pharmaceutical Technology, Ghent University,9000 Ghent, Belgium
[2]Drug Research Unit Ghent, Ghent University Hospital, 9000 Ghent, Belgium
[3]Department of Obstetrics & Gynaecology, Ghent University Hospital, 9000 Ghent, Belgium
[4]Laboratory for Bacteriology Research, Ghent University, 9000 Ghent, Belgium
[5]Heymans Institute of Pharmacology, Ghent University, 9000 Ghent, Belgium

Background: Vaginal drug delivery is a promising route for local and systemic drug delivery. Despite the promising characteristics of the vagina for drug therapy, the development of a suitable vaginal delivery system remains an issue of concern. In this study pellets were evaluated as novel vaginal drug delivery system, with the aim to achieve an acceptable retention time combined with a uniform spreading over the vaginal epithelium.
Materials and methods: Five clinical trials were done with healthy volunteers (five volunteers in each group). Two pellet formulations and one powder formulation were administered: non-disintegrating microcrystalline cellulose (MCC) pellets, fast-disintegrating starch pellets (containing 5% riboflavin sodium phosphate (RSP) as marker) and a freeze-dried lactose/milk powder (containing 5% RSP as marker). These products were administered using hydroxypropylmethylcellulose (HPMC) or hard gelatine capsules. Distribution and retention of the multi-particulate formulation was monitored by colposcopy and swabbing.
Results: Capsule disintegration in the vagina was slow. MCC pellets clustered around the fornix 3h after administration and after 24h only a few pellets were detected in the vaginal cavity. In contrast, starch-based pellets already started to disintegrate 6h after administration, resulting in a complete coverage of the vaginal mucosa after 24h in 8 out of 10 volunteers. The powder formulation had a better distribution after 6h, although after 24h almost no powder remained in the vagina. These results were confirmed by swabbing to determine the amount of RSP (used as a marker) distributed in the different vaginal regions. During the trials only minor side effects were reported by the subjects.
Conclusion: Disintegrating starch-based pellets are a promising new vaginal drug delivery system, which resulted in complete coverage of the vaginal mucosa. A drawback of the pellet formulation was the slow disintegration time of the capsules, which could be eliminated using a different applicator that does not require packing the pellets in capsules for vaginal delivery.

P-09

STRATIFIED PHASE II TRIAL OF CETUXIMAB IN PATIENTS WITH RECURRENT HIGH-GRADE GLIOMA

Sadones J., Joosens E., Bouttens F., Verbeke L., Baurain J-F., D'Hondt L., Strauven T., Chaskis C., In't Veld P., Michotte A., De Greve J., Neyns B.
Oncologisch Centrum, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium

Purpose: To evaluate the antitumor activity and toxicity of single-agent cetuximab in patients with progressive high-grade glioma (HGG) after failure of surgery, radiation-, and chemotherapy.
Patients and methods: Two-arm open-label, phase II study in which patients were stratified according to the EGFR gene amplification status determined by fluorescent in situ hybridization on archival tumor material. Patients received cetuximab 400 mg/m^2 intravenously (IV) during 120 minutes on week 1 followed by weekly doses of cetuximab 250 mg/m^2 IV during 60 minutes. The primary end point was the response rate in both study arms separately.
Results: 55 eligible patients (28 with and 27 without EGFR amplification) tolerated cetuximab well. The most common adverse event consisted of skin toxicity (11% with grade 2 and 7% with grade 3), thrombocytopenia (5% with grade 3), and confusion/diminished consciousness (5% with grade 3). Three patients (5.5%) had a partial response and 16 patients (29.6%) had stable disease. The median time to progression was 1.9 months (95% CI, 1.6 to 2.2 months). Whereas the PFS was less than 6 months in the majority (n=50/55) of patients, 5 patients (9.2%) had a PFS on cetuximab of more than 9 months. Median overall survival was 5.0 months (95% CI, 4.2 to 5.9 months). No significant correlation was found between response, survival and EGFR amplification.
Conclusion: Cetuximab was well-tolerated but had limited activity in this patient population with progressive HGG. A minority of patients may derive a more durable benefit but were not prospectively identified by EGFR gene copy number.

P-10

THE BELGIAN CENTRE FOR PHARMACOTHERAPEUTIC INFORMATION (BCFI/CBIP): PAST, PRESENT AND FUTURE

Christiaens T., De Loof G., Maloteaux JM
Belgian Centre for Pharmacotherapeutic Information, Brussels B-1060 and Gent B-9000 Belgium

There is a plethora of drug-related information towards health professionals and the public, but there is a need for validated and easily accessible sources.

Since more than 30 years, the Belgian Centre for Pharmacotherapeutic Information promotes rational use of medication by providing information to Belgian health professionals and future professionals via a monthly bulletin (Folia Pharmacotherapeutica), and a yearly drug formulary; more recently Transparency brochures have been introduced. While in the first years only written information was provided, gradually electronic communication has also been used in order to allow more rapid access to updated information, but also to permit easy retrieval and integration in the IT systems of health professionals. The website (www.cbip.be) gives access to our information, and provides comparison of prices and reimbursement conditions. Those interested can subscribe to an alert service (“Folia Express”) which informs them about important new drug-related topics.
The challenge for the future is to further improve the quality of the information (based on evidence and, where needed, opinion), with focus on daily practice and accessibility, and with regular updating.
The Centre is currently trying to adapt its information in regard to prescribing based on INN, and electronic prescribing. It will in the near future set up a system for e-learning and provide information aimed specifically to the public, in collaboration with the FAGG-AFMPS.

P-11

EFFECTS OF SIDESTREAM CIGARETTE SMOKE EXTRACT AND HOMOCYSTEINE ON VASCULAR ENDOTHELIAL FUNCTION

Labranche N.[1], Berkenboom G.[2,] Fontaine J.[1] and Pochet S.[1]
[1]Laboratory of Physiology and Pharmacology, Institute of Pharmacy, Université Libre de Bruxelles (ULB), 1050 Brussels, Belgium; [2]Department of Cardiology, Erasme Hospital, Université Libre de Bruxelles (ULB), 1070 Brussels, Belgium.

Background: Recent studies have shown that passive smoking impairs vascular endothelial function, but the underlying mechanism has not been totally elucidated. Furthermore, cigarette smoking is known to be associated with an increased plasma homocysteine (Hcy) level. *Aim*: We investigated if the endothelial dysfunction caused by sidestream cigarette smoke extract (CSE) was due to a nicotine-dependent mechanism. We also decided to compare the effects of cigarette smoke extracts on vasomotor response to those of homocysteine. *Methods*: CSE was prepared as follows: the cigarette was lit under a Plexiglas box connected to a test tube containing 2ml of phosphate-buffered saline. We studied the endothelial-dependent relaxation in isolated rat aortas incubated for 2 hours with 400µl of CSE in presence or in absence of α-bungarotoxin (1µM), an antagonist of nicotinic acetylcholine (Ach) receptor. We also incubated rat aortas with pure nicotine (0.01, 0.1, and 1mM), DL-Hcy (0.1mM) or L-Hcy (0.1mM). *Results*: Exposure to 400µl of CSE caused a decrease in the endothelium-dependent relaxations to Ach from 97,8±1,7% to 78,4±4,3% (% inhibition of phenylephrine-induced plateau, $p < 0,001$). Coincubation with α-bungarotoxin showed no significant change compared with CSE. Moreover, concentration-response curves to Ach remained unaltered in preparations incubated with 0.01 and 0.1mM of nicotine. L-Hcy and DL-Hcy had no significant effect on the response to Ach. *Conclusions*: Our results suggest that the acute endothelial toxicity of passive smoking cannot simply be ascribed to a nicotine-dependent mechanism. We also conclude that, even if cigarette smoke leads to mildly elevated homocysteine levels, it does not show any acute toxicity on vascular endothelial function at those plasma concentrations.

P-12

OLFACTORY FUNCTION IN EARLY BLIND HUMANS: PSYCHOPHYSICAL TESTING AND CEREBRAL CARTOGRAPHY

Cuevas I.[1], Plaza P.[1], Rombaux P.[2], Delbeke J.[1], Collignon O.[1]; De Volder A.G.[1], Renier L.[1]
[1] Neural Rehabilitation Engineering Laboratory, Université catholique de Louvain, Brussels, Belgium.
[2] Department of Otorhinolaryngology, Université catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

Previous studies provided demonstration of functional reorganization of the occipital cortex in early blind (EB) humans, associated to superior abilities in the use of their remaining senses. While auditory and tactile functions have been investigated for long time, little is known about olfactory function in this population. The purpose of this study was to investigate the potential effects of congenital blindness on olfactory abilities, as well as, the brain areas recruited during odor stimulation. Eight EB and eight sighted control participants were tested using the *Sniffin's Sticks Test* ® and a retronasal olfactory test. The cerebral cartography was obtained by *Low Resolution Electromagnetic Tomography* (LORETA®) through Event-Related Potentials (ERPs) recorded in response to olfactory stimulation with 2-Phenyl ethyl alcohol and to trigeminal stimulation with CO2. Psychophysical testing indicated that EB subjects obtained better scores for "odor detection threshold *"* ($p=0.017$) and "odor discrimination" ($p < 0.05$). The cerebral cartography revealed similar activation of the occipital cortex in the two groups of subjects and a posterior shift of brain activity in EB subjects, significant for trigeminal responses in the precuneus (BA 7). These findings suggested that early blind subjects have an advantage in odor detection and react with a recruitment of posterior brain areas to odor stimulation, mainly during a somato-sensory stimulation in the sense of smell.

P-13

SPATIAL AND NON-SPATIAL PROCESSING OF SOUNDS AND VIBRO-TACTILE STIMULI IN THE OCCIPITAL CORTEX OF EARLY BLIND HUMANS

Renier L.A.[1,2], Anurova I.[1,3], De Volder A.G.[2], Carlson S.[3], Rauschecker J.P.[1]
[1] Laboratory for Integrative Neuroscience and Cognition, Georgetown University;
[2] Neural Rehabilitation Engineering Laboratory, Université Catholique de Louvain;
[3] Institute of Biomedicine/Physiology, University of Helsinki, Finland

It has been shown that the reorganized occipital cortex of early blind subjects (EBS) was recruited during spatial and non-spatial processing of sounds and tactile stimuli. However, little is known about how this cortex is functionally organized in EBS. Using fMRI in twelve EBS and twelve matched sighted control subjects (SCS), we compared the pattern of activation elicited by the detection, the identification and the localization of sounds and vibro-tactile stimuli in the same subjects. Results showed an opposite pattern of activation/deactivation in the middle occipital gyrus (MOG, BA37) during the auditory and tactile conditions, i.e. activation in EBS and deactivation in SCS. Contrasts between the auditory and the tactile modality and the different tasks in EBS did not reveal any double dissociation between the modalities nor the tasks in the occipital cortex. However, the MOG and the lingual gyrus (LG, BA18) were recruited to a different extent according to the task: the localization conditions generated the highest bold signal whereas the detection conditions produced the lowest bold signal in these regions. The pattern of activation/deactivation suggests that visual deprivation leads to a reattribution of function of the occipital cortex, but that the connections between this cortex and the auditory and somatosensory cortices already exist in SCS. The task-dependent modulation suggests a functional specialization of the occipital cortex to support the functions that represent a high ecological and practical value for EBS. This leads us to hypothesize that environmental constraints and EBS's daily life experience determine the functional organization visually deprived areas.

P-14

INSULIN AND ALDOSTERONE INCREASE SODIUM TRANSPORT ACROSS A6 CELL MONOLAYERS BY ACTIVATING HYDROGEN PEROXIDE PRODUCTION

Markadieu N.[1](1), Crutzen R.[1] (1), Boom A.[1] (1), Erneux C.[2] (2), Beauwens R.[1]
[1]Laboratory of Cell and Molecular Physiology, [2]Interdisciplinary Research Institute. Université Libre de Bruxelles, Campus Erasme, 808 Route de Lennik, 1070 Bruxelles, Belgium

Insulin and aldosterone are major hormones controling sodium reabsorption in the distal nephron, hence controlling also extracellular fluid volume and blood pressure. We have demonstrated that insulin and aldosterone as well as hydrogen peroxide induce the generation of phosphatidylinositol 3,4,5-*tris*phosphate (PIP_3) and a rise in sodium transport. The aim of the present study was to investigate whether the stimulation of the PI 3-kinase pathway could result from local hydrogen peroxide production. We incubated A6 cell monolayers with the oxidation-sensitive fluorescent probe 5,6-chloromethyl-2´,7´-dichlorodihydrofluorescein diacetate (CM-H_2DCF-DA) under various experimental conditions. Insulin induced an immediate increase in fluorescence, indicative of ROS production that begins within two minutes after insulin stimulation was maximal at 5 min and lasted at least 30 min. Aldosterone induced an increase in fluorescence that begins 30 min after aldosterone addition, was maximal at 50 min and lasted for 24 hr. In both cases the increase in fluorescence was inhibited by a chelator of $O_2^{\bullet -}$ (Nitro Blue Tetrazolium, 100 µM) and by a chelator of H_2O_2 (ebselen, 50 µM), These drugs also inhibited the rise in sodium transport induced by both hormones. Several inhibitors of the NADPH oxidase (Nox) enzymes (diphenyleneiodonium, phenylarsine oxide and plumbagin) also inhibited both the generation of ROS and the stimulation of sodium transport induced either by insulin or by aldosterone. In conclusion the present results support the hypothesis that activation of some Nox enzyme is responsible for increased hydrogen production, PI 3-kinase activation leading to increased sodium transport following exposure to either insulin or aldosterone.

P-15

DIFFERENT ACTIVATION OF ERM PROTEINS BY PKC AND RHO KINASE IN VASCULAR SMOOTH MUSCLE

Baeyens N.[1], Horman S.[2] and Morel N.[1]
[1]Laboratoire de physiologie cellulaire, [2]Laboratoire de pathologie cardiovasculaire, UCL, 1200 Bruxelles, Belgium.

ERM (Ezrin, Radixin & Moesin) proteins are known to be linkers between the actin cytoskeleton and membrane proteins. We have investigated the activation of these proteins in intact rat aorta by using a phospho-ERM antibody and Western-Blot technique. Stimulation with noradrenaline (1μM) rapidly increased ERM phosphorylation, which was maximum at 2 min and slightly decreased at 10 min. ERM proteins were also phosphorylated by 100 mM KCl stimulation with a maximal phosphorylation after 30 s and a fast decrease after longer stimulation, indicating that ERM proteins can be phosphorylated by different pathways. The inhibitor of Rho kinase (Y27632 10 μM), totally inhibited ERM phosphorylation measured after 2 and 10 min of noradrenaline stimulation but did not affect the rapid increase (30 s) in ERM phosphorylation induced either by noradrenaline or high KCl. The rapid increase in ERM phosphorylation induced by KCl stimulation was completely inhibited by 1 μM nimodipine, a blocker of voltage-gated calcium channels. Furthermore, ionomycin, a calcium ionophore, induced a rapid increase in ERM phosphorylation. Moreover, GÖ6983, an inhibitor of calcium-activated PKC, totally inhibited the fast ERM phosphorylation evoked either by noradrenaline or KCl stimulation but not the phosphorylation induced by a longer stimulation with noradrenaline. These results indicated that ERM proteins were phosphorylated in vascular smooth muscle in response to agonist or depolarising stimulation. This phosphorylation consisted in two different phases: a fast calcium dependent phosphorylation induced by PKC and a much slower calcium independent phosphorylation induced by Rho kinase.

P-16

ANTI-EPILEPTIC EFFECTS OF VAGUS NERVE STIMULATION IN THE FOCAL PILOCARPINE MODEL

Mollet L.[1], Clinckers R.[2], Raedt R.[1], Meurs A.[1], Wyckhuys T.[1], Van Dycke A.[1], El Tahry R.[1], Vonck K.[1], Wadman W.[3], Michotte Y.[2], Smolders I.[2], Boon P.[1]

[1] Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital, Belgium, [2] Department of Pharmaceutical Chemistry, Drug Analysis and Drug Information, Research Group Experimental Pharmacology, Vrije Universiteit Brussel, Belgium**,** [3] Swammerdam Institute of Life Sciences, Department of Neurobiology, University of Amsterdam, Amsterdam, The Netherlands

Purpose: Although vagus nerve stimulation (VNS) is an approved treatment for patients with refractory epilepsy, its mechanism of action is still unclear. Enhancement of noradrenalin release in the hippocampus, caused by altered activity in the locus coeruleus, might contribute to the anti-convulsive effect of VNS. The aim of this study was to evaluate the effects of VNS on pilocarpine-induced limbic seizures and on hippocampal extracellular neurotransmitter concentrations in vivo in rats.

Methods: Rats (n=14) were implanted with a stimulation electrode around the left vagal nerve. Depth EEG electrodes and a microdialysis probe were stereotactically inserted into the left hippocampus. One week after surgery EEG recording and microdialysis was started. Two hours after the start of the experiment VNS was initiated in half of the rats and continued until the end of the experiment. Two hours after VNS initiation, limbic seizures were evoked in both the control and stimulated group by intrahippocampal administration of pilocarpine via the microdialysis probe. Behavioral changes indicative of seizure activity and hippocampal EEG were monitored. Concentration of noradrenalin, dopamine, serotonin and GABA were measured.

Results: In the stimulated group, the scores of behavioral seizures were significantly ($p<0.01$) reduced compared to control (median 3 vs. 12 in the control group). VNS did not attenuate the latency to pilocarpine-induced limbic seizures but significantly reduced the duration of the seizures (54 ± 37 min vs. 101 ± 23 min in the control group). Moreover, VNS resulted in a significant increase in hippocampal extracellular noradrenalin, but had no effect on dopamine, serotonin and GABA levels.

Conclusion: Vagus nerve stimulation (VNS) induces a rapid increase in hippocampal extracellular noradrenalin concentration and a reduction in behavioral scores and duration of pilocarpine-induced limbic seizures. It needs to be investigated whether there is a causal relationship between the increased noradrenalin concentration and the anticonvulsant effect of VNS.

P-17

LOCAL INFUSION OF NEUROPEPTIDE Y HAS ANTI-EPILEPTIC EFFECTS IN FULLY KINDLED RATS

Dauwe I.[1], Raedt R.[1], Van Dycke A.[1], Meurs A.[1], Wyckhuys T.[1], El Tahry R.[1], Vonck K.[1], Wadman W.[2], Boon P.[1]

[1] Laboratory of Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital, Ghent, Belgium, [2] Swammerdam Institute of Life Sciences, Department Neurobiology, University of Amsterdam, Amsterdam, The Netherlands

Purpose: Due to the high number of medically untreatable patients, developing new therapies for temporal lobe epilepsy remains a challenge. Local delivery of anti-epileptic substances in the ictal onset region is a promising technique because of its benefit that systemic side effects can be avoided. In this study we evaluate the anti-epileptic effect of local delivery of neuropeptide Y (NPY) in the hippocampus of kindled rats.
Methods: Rats (n=11) were implanted with a bipolar registration electrode in the left hippocampus and a stimulation electrode-cannula complex in the right hippocampus. Once the rats were fully kindled, the cannula was connected to an osmotic minipump to perform continuous intrahippocampal delivery (0.47 µl/h). A cross-over experiment was performed to compare the effect of local delivery of NPY (2 µg/µl) and saline on kindling characteristics. On every other day during six days of local delivery, afterdischarge threshold, afterdischarge duration and seizure severity were evaluated.
Results: Comparison of NPY treatment and saline delivery revealed a significant decrease in seizure severity ($p < 0.01$) and a significant reduction of afterdischarge duration ($p < 0.01$). No significant difference was seen in afterdischarge threshold (NPY 542 µA ± 68; saline 389 µA ± 74).
Conclusion: This study proves the anti-epileptic effect of continuous intrahippocampal delivery of neuropeptide Y in fully kindled rats.

P-18

EFFECT OF HIPPOCAMPAL DEEP BRAIN STIMULATION ON BLOOD PERFUSION EVALUATED BY µSPECT

Van Nieuwenhuyse B.[1], Wyckhuys T.[1], Raedt R.[1], Meurs A.[1], Van Dycke A.[1], El Tahry R.[1], Vonck K.[1], Wadman W.[2], Staelens S.[3], Boon P.[1]

[1] Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital, Ghent, Belgium, [2] Swammerdam Institute of Life Sciences, Department of Neurobiology, University of Amsterdam, Amsterdam, The Netherlands, [3] Medical Image and Signal Processing Group, Department of Electronics and Information Systems, Ghent University, Ghent, Belgium

Purpose: Epilepsy is a chronic neurological disorder, affecting 0.5-1% of the population. Temporal Lobe Epilepsy remains one of the most difficult to treat forms of epilepsy, as one third of all patients remains refractory to anti-epileptic drugs. Hippocampal deep brain stimulation (DBS) is a promising experimental approach to treat TLE. However, the precise mechanism of action is unknown and may possibly hamper the therapeutic potential of DBS. Neuro-imaging by means of Single Photon Emission Computed Tomography (SPECT) is a non-invasive manner of evaluating regional cerebral blood flow (rCBF) changes, which are assumed to reflect changes in neural activity that are induced by DBS.

Methods: Rats (n=6) were implanted with a DBS electrode in the right hippocampus. After recovery from surgery, rats received multiple injections with 10mCi HMPAO-$Tc99^{m}$ either during application of hippocampal DBS or during sham stimulation. Consequently, the rats were anesthetized with isoflurane and small animal SPECT scans of the brain were taken and manually co-registered with MRI images of the same rats. Acquired µSPECT images were evaluated by means of subtraction analysis between DBS and sham stimulated brain images.

Results: Unilateral hippocampal DBS caused significant changes in rCBF, both ipsi- and contralaterally to the DBS electrode. The changes in rCBF were seen in structures important in seizure control such as hippocampus, entorhinal cortex, piriform cortex. Additionally, the amplitude and extension of the induced rCBF changes could be correlated with different stimulation paradigms.

Conclusion: Small animal SPECT is a feasible technique to visualize significant increases and decreases in regional cerebral blood flow caused by hippocampal DBS. Changes in blood perfusion were mainly associated with structures involved in seizure control. Our results promote further research on DBS using small animal SPECT in rats.

P-19

ADENOSINE SECRETION BY NEURAL STEM CELLS ISOLATED FROM ADK-/- MICE

Van Dycke A.[1], Raedt R.[1], Boison D.[2], Verstraete A.[3], Meurs A.[1], Wyckhuys T.[1], El Tahry R.[1], Vonck K.[1], Wadman W.[1,4], Boon P.[1] ([1,3]UGent, [2]RS Dow Labs Portland USA, & [4]Univ. Amsterdam NL.)

[1]Laboratory for Clinical and Experimental Neurophysiology, Department of Neurology, Ghent University Hospital, Ghent, Belgium, [2]Robert Stone Dow Neurobiology Laboratories, Legacy Research, Portland, USA, [3]Laboratory of Clinical Biology, Ghent University Hospital, Ghent, Belgium, [4]Swammerdam Institute of Life Sciences, Department of Neurobiology, University of Amsterdam, Amsterdam, The Netherlands

Purpose: There is an ongoing search for alternative treatment options for patients with refractory epilepsy. Local intracerebral delivery of anti-epileptic compounds may represent a novel strategy with specific advantages such as the option of higher local doses and reduced side effects. Adenosine is a good candidate for local delivery since it has proven anti-epileptic effects. Neural stem cells isolated from adenosine kinase deficient (Adk-/-) mice overexpress adenosine and may be a source for long-term local delivery. We evaluated the amount of adenosine secretion compared to control cells isolated from C57 Black 6 mice (C57BL/6).

Methods: Foetal neural stem cells were isolated from Adk-/- and C57BL/6 p14 mice foetuses. Stem cells were cultured and expanded in vitro for several weeks. Then cells were plated at different densities (10.000 and 100.000 cells/cm²) during 24 hours. Medium was replaced and samples (200µl) were taken at different time points (after 1 h, 2h, 4h, 8h, 12h and 24h). The same was done with cells plated at a density of 50.000/cm² that were allowed one week of differentiation. The different samples were analyzed to measure the amount of adenosine release with Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS).

Results: Adk-/- cells secreted more adenosine compared to control cells at any time point. After 24h 507ng per 100.000 cells was secreted by Adk-/- cells compared to 40ng per 100.000 cells by control cells. The Adk-/- cells plated at a density of 10.000 cells/cm² secreted 10 times less compared to the cells plated at 100.000/cm². Differentiated cells released less adenosine: 89ng (Adk-/-) per 50.000 cells after 24h, but this was also higher compared to the control cells.

Conclusions: Foetal neural stem cells isolated from Adk-/- mice release significantly more adenosine compared to control cells isolated from C57BL/6 mice. Compared to studies concerning local delivery of adenosine, both non-differentiated and differentiated Adk-/- cells release enough adenosine in vitro per 24h to be a tool for long-term local intracerebral adenosine delivery as a therapy for refractory epilepsy.

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