



**7th GRADUATE COURSE
ON
NEUROPSYCHOPHARMACOLOGY**

OCTOBER 7-15, 2010



CONTENTS

CONTENTS	3
PREFACE	5
PROGRAM	7
VENUES / ROUTE DESCRIPTIONS	15
ABSTRACTS	17
PARTICIPANTS	51

PREFACE

This 7th graduate Neuropsychopharmacology course, designed for PhD students and postdocs in the field of neurosciences, is organized by the Graduate School Neurosciences Amsterdam Rotterdam, the Rudolf Magnus Graduate School of Neurosciences (Utrecht) and the Centre for Human Drug Research (Leiden). The course addresses our current understanding of the pharmacology of CNS active drugs, the discovery of CNS drug targets as well as the development of innovative medicines, allowing students to become familiar with the fascinating field of neuropsychopharmacology. In this respect, the major classes of pharmacotherapeutics for the clinical management of various neurological and psychiatric diseases and the pathological mechanisms of these brain disorders will be discussed.

Each day addresses a particular type of neurological or psychiatric disorder from basics to bedside. Lectures are primarily scheduled in the mornings. The afternoon sessions include demonstrations, site visits and special lectures. **Keynote lectures**, that are open to all interested scientists, are scheduled at the end of the day and will be presented by leading experts in the field.

The different topics of the course will be presented at different locations in Amsterdam, Utrecht and Leiden. Travel instructions and local maps are included in the reader.

Attendance of all lectures is mandatory and will be honoured with a certificate. **Accreditation** covers 56 hours in the graduate teaching programs on neuroscience.

If you would not be able to attend a specific activity, we trust that you will notify Prof. A.N.M. Schoffemeer (anm.schoffemeer@vumc.nl).

We hope that you will appreciate this course,

The organizing committee,

Dr. B. Drukarch

Dr. M.A.F.M. Gerrits

Prof.dr. J. van Gerven

Prof.dr. A.N.M. Schoffemeer (chair)

Prof.dr. D.J. Veltman

Dr. H.E. de Vries

Prof.dr. W.J. Wadman

PROGRAM
COURSE ON NEUROPSYCHOPHARMACOLOGY
October 7-15, 2010

Topics and places

October 7	Basic principles	Amsterdam	NIN
October 8	Psychotic disorders	Utrecht	UMCU
October 11	Neurodegenerative disorders	Amsterdam	NIN
October 12	Affective disorders	Amsterdam	NIN
October 13	Question-based development of CNS-active drugs	Leiden	CHDR
October 14	Epilepsy	Amsterdam	UvA
October 15	Addiction	Amsterdam	VUmc

Thursday 7 October 2010: "Basic principles"

Venue: Lecture room, Netherlands Institute for Neuroscience, Meibergdreef 47, Amsterdam-ZO

Coordinator: A.N.M. Schoffemeer (VUmc)

08.30 - 09.00: Introduction and registration
A.N.M. Schoffemeer, VUmc

09.00 - 10.00: Functional neuroanatomy
P. Voorn, VUmc

10.00 - 10.15: Coffee/tea

10.15 - 11.15: Targeting G-protein coupled receptors
R. Leurs, VU

11.15 - 12.15: The brain as drug target
A.G. de Boer, LACDR

12.15 - 13.30: Lunch (not provided)

Venue:

13.30 - 14.30: PET in drug development
A.A. Lammertsma, VUmc

14.30 - 15.30: **Keynote lecture**
Rational design of ligands for nicotinic acetylcholine receptors
A.B. Smit, VU

Friday 8 October 2010: "Psychotic disorders"

Venue: University Medical Center Utrecht (room Unnik Groen in the W.C. van Unnik building at the Uithof, Heidelberglaan 2, Utrecht)

Coordinator: M.A.F.M. Gerrits (UMCU)

- 09.00 - 10.00: First psychotic episode: symptoms, classification, treatment and brain morphology
W. Cahn, UMC Utrecht
- 10.00 - 11.00: Antipsychotics: mechanism of action and pharmacological profiles
T. Werkman, UvA.
- 11.00 - 11.15: Coffee/tea
- 11.15 - 12.15: Animal models of antipsychotic drug research
B. Ellenbroek, Evotec, Hamburg, Germany
- 12.15 - 13.15: Gray and white matter density changes in schizophrenia
H. Hulshoff-Pol, UMC Utrecht
- 13.15 - 14.00: Lunch (provided)
- 14.00 - 16.00: Site visit brain imaging, max 15 personen
H. Hulshoff-Pol, UMC Utrecht

Monday 11 October 2010: “Neurodegenerative disorders”

Venue: Lecture room, Netherlands Institute for Neuroscience, Meibergdreef 47, Amsterdam-ZO

Coordinators: H.E. de Vries (VUmc) and B. Drukarch (VUmc)

09.00 - 09.15:	Introduction
09.15 - 10.00:	Multiple Sclerosis pathogenesis 2010: where are we now? J. van Horssen, VUmc
10.00 - 10.45:	Therapeutic targets for Multiple Sclerosis H.E. de Vries, VUmc
10.45 - 11.15:	Coffee/tea
11.15 - 12.00	Dysregulation of impulse control and pharmacotherapy of Parkinson’s disease O.A. van den Heuvel, VUmc
12.00 - 12.45:	Partial dopamine D2 receptor agonists in Parkinson’s disease E. Ronken (Solvay)
12.45 - 14.00:	Lunch (not provided)
14.00 - 14.45:	Parkinson’s disease: a subcellular movement disorder providing novel therapeutic targets B. Drukarch, VUmc
14.45 - 15.30:	Stimulation of beta-amyloid clearance in therapy of Alzheimer dementia M. Wilhelmus, VUmc
15.30 - 16.00:	Coffee/tea
16.00 - 17.00	Keynote lecture Mechanism based pharmacokinetic / pharmacodynamic (PK/PD) modelling for CNS-active drugs Dr. E. de Lange, LACDR

Tuesday 12 October 2010: "Affective disorders"

Venue: Lecture room, Netherlands Institute for Neuroscience, Meibergdreef 47, Amsterdam-ZO

Coordinator: D. Veltman (VUmc/AMC)

- | | |
|----------------|---|
| 09.00 - 09.10: | Introduction
D.J. Veltman, VUmc/AMC |
| 09:10 - 10:05: | Clinical features and treatment of bipolar disorder
R. Kupka, VUmc/Altrecht |
| 10:05 - 11:00: | Major depressive disorder: clinical and neurobiological aspects
A.H. Schene, AMC |
| 11:00 - 11:20: | Coffee/tea |
| 11:20 - 12:15: | Animal models for depression: opportunities and limitations
L. Groenink, UU |
| 12:15 - 13:30: | Lunch (not provided) |
| 13:30 - 14:25: | Neuropsychopharmacology of today's and future antidepressants
T. Steckler, Janssen Pharmaceutica, Beerse |
| 14:25 - 15:20: | Imaging antidepressants: visualizing mechanisms of action
H.G. Ruhé, AMC |

Wednesday 13 October 2010: “Question-based development of CNS-active drugs”

Venue: Centre for Human Drug Research, Zernikedreef 10, 2333 CL Leiden

Coordinators: J.M.A. van Gerven and G.J. Groeneveld (Centre for Human Drug Research)

- 08.30 - 09.00: Welcome and coffee/tea
Introduction
- 09.00 - 09.45: CNS drug development: from phases to questions
A.F.Cohen, Leiden
- 09.45 - 10.30: Case: Migraine - from genes to mouse model and drug target
M.D. Ferrari, Leiden
- 10.30 - 10.45: Coffee/tea
Answering questions in early CNS drug development
- 10.45 - 11.30: What is the dose range for first-in-human administration?
Investigators' brochure and animal-to-human predictions
J.M.A.van Gerven, Leiden
- 11.30 - 12.15: Does the drug enter the central nervous system?
Pharmacokinetics and pharmacodynamics of BBB-penetration
G.J. Groeneveld, Leiden
- 12.15 - 13.00: Does the drug have its anticipated pharmacological effects?
Pharmacological biomarkers and challenge tests
J.M.A. van Gerven, Leiden
- 13.00 - 14.00: Lunch (provided)
- 14.00 - 14.45: Does the drug have meaningful (patho)physiological effects?
Translational disease models and disease models
G.J. Groeneveld, Leiden
- 14:45 - 15:00: Coffee/tea
- 15.00 - 17.00: Laboratory visits
NeuroCart and PainCart demonstrations

Thursday 14 October 2010: "Epilepsy"

Venue: CWI - Turing Zaal, Science Park 123, Amsterdam

Coordinator: W.J. Wadman (UvA)

- | | |
|----------------|--|
| 09.30 - 10.30: | Clinical aspects of epilepsy
A. Gaitatzis (SEIN, Heemstede) |
| 10.30 - 11.30: | Pharmacological modulation of Amino Acid mediated synaptic transmission
R. Voskuyl, RUL |
| 11.30 - 12.30: | Strategies to prevent or stop the progression of epilepsy or
pharmacoresistance in epilepsy
J. Gorter, UvA |
| 12:30 - 13:30 | Lunch (not provided) |
| 13.30 - 14:15: | Local delivery and cell therapy in refractory epilepsy
R. Raedt, AZG, Gent |
| 14.15 - 15.00: | Pharmacology of ion channels in epilepsy
Wytse Wadman, UvA |
| 16.00 - 17.00: | Keynote lecture
How does the brain become epileptic?
Tallie Baram (Irvine, USA) |

Friday 15 October 2010: "Addiction"

Venue: De Maas (VUmc – ZH 4 E11), Van der Boechorststraat 4, Amsterdam

Coordinator: A.N.M. Schoffelmeer (VUmc)

- 08.45 - 09.45: Addiction: new treatment options
W. van den Brink, UvA/AMC
- 09.45 - 10.45: Kicking the habit-automatic behaviours in drug addiction
L.J.M.J. Vanderschuren, UMCU
- 10.45 - 11.00: Coffee/tea
- 11.00 - 12.00: Impulsivity as a risk factor for addiction
T. Pattij, VUmc
- 12.00 – 13.00: Prefrontal cortex plasticity mechanisms in heroin seeking and relapse
S. Spijker, VU
- 13.00 - 14.00: Lunch (not provided)
- 14.00 – 15.00: **Swammerdam Lecture**
A. Araque, Cajal Institute, Madrid
Tripartite synapses: Astrocytes process and control synaptic information
host: E. Aronica, UvA/AMC
- 15.00 - 16.00: Certificates of attendance and drinks!

VENUES / ROUTE DESCRIPTIONS

October 7, 11 and 12, 2010

NETHERLANDS INSTITUTE FOR NEUROSCIENCE, lecture room, 3rd floor

Meibergdreef 47, Amsterdam-Zuidoost

<http://www.nin.knaw.nl/information/route/>

October 8, 2010

UNIVERSITY MEDICAL CENTER UTRECHT (ROOM UNNIK GROEN IN THE W.C. VAN UNNIK BUILDING AT THE UITHOF IN UTRECHT), Heidelberglaan 2, Utrecht

Dutch: <http://idc.fss.uu.nl/dmdocuments/Routebeschrijving%20Van%20Unnikgebouw.pdf>

English: <http://www.uu.nl/faculty/geosciences/en/Contact/Pages/adresenroute.aspx>

October 13, 2010

CENTRE FOR HUMAN DRUG RESEARCH, ZERNIKEDREEF 10, LEIDEN

<http://www.proefpersoon.nl/default.asp?id=905>

October 14, 2010

Centrum voor Wiskunde en Informatica (CWI-UvA) – Turingzaal, Science Park 123, Amsterdam

http://homepages.cwi.nl/~schaefer/agt10/map_science_park.pdf

<http://www.cwi.nl/en/general/Address>

October 15, 2010

VU UNIVERSITY MEDICAL CENTER, ROOM DE MAAS = ZH 4 E 11 (HOSPITAL)

Address: **Van der Boechorststraat 4, Amsterdam**, use the stairs to the 4th floor

<http://www.vumc.com/patientcare/477446/>

(Please note that you can also get to the stairs through the hospital, De Boelelaan 1117, Amsterdam.)

VU University medical center, pantry = ZH 2 E (hospital)

Address: **Van der Boechorststraat 4, Amsterdam**, 2 floors down from ZH 4 E 11

(please see above.)

ABSTRACTS

FUNCTIONAL ANATOMY

P. Voorn

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Functional neuroanatomy allows us to elucidate the neural correlates of neuropsychiatric disorders by describing how brain damage or neuroanatomical modifications can lead to disturbances in mental health. Destruction of brain regions may occur as a consequence of trauma or neurodegenerative disease such as Alzheimer's or Parkinson's disease. The most famous case describing a relationship between trauma and cognitive changes is perhaps that of Phineas Gage, who suffered severe damage in the frontal and temporal lobes. To this day, 160 years after the fact, the extent of the lesions in Gage's brain are still being studied. Why then is correlating structure to function proving to be so elusive? One reason is the sheer complexity of the neural systems that the trauma- or disease-affected brain regions are part of. At first sight, the multi-faceted disturbances in mental health that are seen in Parkinson's disease or drug addiction seem at odds with the restricted number of brain regions affected in these disorders. In both, the dopaminergic system is known to play a crucial role, perhaps *the* crucial role. Dopamine may regulate motor/sensory processes as well as cognitive activity via its influence on the corticostriatal system. However, the latter system is organized in a parallel fashion, with separate channels processing limbic information, highly processed "associational" information or sensory-motor information¹. For behavior to occur in its full complexity, limbic activities must interface with sensory-motor systems and with prefrontal cognitive-executive circuits as well as other association cortex systems. Thus, communication is required between the different, parallel cortico-striatal subsystems. Lesions or manipulations in different system components may result in similar neuropsychiatric deficits, complicating our functional interpretation. It is, therefore, essential to "know your *system* before manipulating it". The relevance of the parallel organization of the corticostriatal system will be discussed with respect to aspects of drug addiction and the cognitive disturbances in Parkinson's disease. Special attention will be given to recent advances in our anatomical understanding of regulation of dopamine neurotransmission².

References

1. Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci.* 27 (8): 468-474 (2004).
2. Matsumoto M, Hikosaka O (2009) Representation of negative motivational value in the primate lateral habenula. *Nat Neurosci.* 12 (1): 77-84.

TARGETTING G-PROTEIN COUPLED RECEPTORS

R. Leurs

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Cells process information conveyed to them as extracellular signals such as hormones, neurotransmitters, autacoids, growth factors, odorants and light, and transduce the extracellular stimuli into a profound intracellular biochemical response. Many extracellular signaling molecules bind to membranous receptors that represent one element of a three component transmembrane signaling system consisting of a receptor, a heterotrimeric guanine-nucleotide-binding (G) protein, and an effector. These receptors, generally known as GPCRs, are encoded by the fourth largest gene family in man and comprise up to 1% of the human genome, and form an extraordinary superfamily of receptor molecules that participates in many physiological processes, including synaptic neurotransmission, the perception of light, taste, olfaction and pain, as well as immune functions, and cell division. Because of their pivotal role in physiology, GPCRs are a major focus of drug development and currently approximately 50% of all therapeutics target GPCRs .

GPCRs are relatively easily amenable to drug development due to their transmembrane localization, which alleviates the need for drugs to enter the cells in order to be effective, explaining why GPCRs have become such successful drug targets. The superfamily of GPCRs consists of transmembrane proteins sharing a highly similar architecture: an extracellular amino terminus, three extra-cellular and three intracellular loops, and seven trans-membrane alpha-helices that connect the extra- and intra-cellular loops. GPCRs contain an extracellular ligand-binding site, critical to their differential activation, as well as intracellular domains for coupling to proteins, such as G proteins.

While ligands are usually considered as the main regulators of GPCR activity, the functioning of GPCRs may also be regulated in other ways. GPCR mediated signaling also depends on the cellular context. The mechanism by which GPCRs translate extracellular signals into intracellular biochemical changes was initially envisioned to depend highly on G-protein coupling. Yet, recently described multidomain scaffolding proteins and GPCR interacting accessory/chaperone molecules, including GPCR themselves as homo- or heterodimers, and ion-channels, provides new ways for diverse molecular mechanisms governing ligand recognition, signaling specificity, and receptor trafficking

References:

- Gurevich VV., Gurevich E.V. (2008) How and why do GPCRs dimerize? *Tr. Pharmacol Sci.* 29: 234-240.
- Lagerström M.C., Schiöth H.B. (2008) Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat. Rev. Drug Discov.* 7:339-357.
- Luttrell L.M. (2008) Reviews in molecular biology and biotechnology: transmembrane signaling by G protein-coupled receptors. *Mol. Biotechnol.* 39:239-264.

THE BRAIN AS DRUG TARGET

A.G. de Boer

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The central nervous system (CNS) is a sanctuary site and is protected by various barriers including the blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier (BCSFB) and the barrier between brain tissue and the CSF called the ependyma. These regulate brain homeostasis and the transport of endogenous and exogenous compounds by controlling their selective and specific uptake, efflux and metabolism in the brain. The BBB is the most important barrier for drug transport to the brain since its surface area is similar as the BCSFB but faced to the blood-side. Unfortunately, many potential drugs for the treatment of most brain diseases are not able to cross the BBB. As a result, various drug delivery and targeting strategies are currently being developed to enhance the absorption and distribution of drugs into the brain. Moreover, diseases may influence the functionality of the BBB and influence therefore drug transport to the brain also. This presentation focuses on the biology and physiology of the blood-brain barrier with respect to drug transport (absorption, distribution) and the possibilities to deliver large molecular drugs (by receptor-mediated non-viral drug delivery) to the (human) brain.

These will include:

- **Physico-chemical factors related to the drug:** lipid solubility; electrical charge; mol. weight (size)
- **Physiological aspects:** passive (para- vs transcellular) transport; active BBB influx- and efflux mechanisms (including multidrug resistance); metabolism
- **Drug targeting to the brain:** invasive delivery (neurosurgical); osmotic opening of the BBB; application of endogenous transport systems (adsorptive-, fluid phase-, carrier-mediated- and receptor-mediated transport) for drug- and gene-targeting.

References

- Abbott, NJ (2005) Dynamics of CNS barriers: evolution, differentiation, and modulation, *Cell Mol. Neurobiol.* 25(1):5-23.
- de Boer AG, Gaillard PJ (2007) Drug targeting to the brain, *Ann.Rev.Pharmacol.Toxicol.* **47**: 323-355.
- Pardridge WM. (2002) Drug and gene targeting to the brain with molecular Trojan horses, *Nat. Rev. Drug Discov.* 1(2):131-9.
- Rip J, Schenk G, de Boer AG, Differential receptor-mediated drug targeting to the brain, *Exp. Opin. Drug Delivery* 2009; 6(3): 227-237.
- Rubin LL, Staddon JM. (1999) The cell biology of the blood-brain barrier. *Annu. Rev. Neurosci.* 22:11-28.

PET IN DRUG DEVELOPMENT

A.A. Lammertsma

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Positron emission tomography (PET) is a tomographic imaging technique, which allows for accurate non-invasive *in vivo* measurements of regional tissue function in man (Phelps, 2004). By using different tracers, a multitude of physiological, biochemical and pharmacological parameters can be measured. These include blood flow (perfusion), blood volume (vascularity), oxygen utilisation, glucose metabolism, pre- and post-synaptic receptor density and affinity, neurotransmitter release, enzyme activity, drug delivery and uptake, gene expression, etc. In fact, PET represents the most selective and sensitive (pico- to nano-molar range) method for measuring molecular pathways and interactions *in vivo* (Jones, 1996). Apart from its capacity to provide new information on human disease, PET is also important for the objective assessment of therapeutic efficacy and could play an important role in the development of new drugs (Lammertsma, 2004).

Within the area of drug development, PET can be used in several ways. Firstly, it can be used in a direct manner by labelling the drug with a positron emitter. This enables direct PET measurements of tissue drug concentrations as function of time, allowing for an assessment whether these concentrations are high enough for therapeutic purposes. This is for assessing uptake of labelled anti-cancer drugs in tumours, which can be compared with uptake in normal tissue (toxicity). A second application is the measurement of perfusion or metabolism following or during treatment. The best example is measurement of tumour glucose metabolism as a marker of response to chemotherapy, which is now an accepted surrogate endpoint in the evaluation of new chemotherapeutic agents.

Drugs developed for neurological and psychiatric diseases usually act through interaction with specific neuroreceptors or enzymes. To assess whether this is indeed the case with a new drug, use is made of existing PET ligands that have been developed specifically for the neuroreceptor or enzyme under investigation. Receptor occupancy or enzyme activity can be measured as function of administered dose of the drug. In addition, biological clearance of the drug can be measured by performing PET scans at various times after drug administration. Due to the excellent test-retest performance of PET, an important consequence is that both optimal dose and dosing regimen can be determined from studies in a limited number (<10) of subjects (Bench *et al.*, 1993; Bench *et al.*, 1995). The optimal dose and dosing regimen can then be used as a starting point in clinical trials. This is in contrast to current practice where the dose for clinical trials often is based on the occurrence of unacceptable side effects.

References

- Bench CJ, Lammertsma AA, Dolan RJ, Grasby PM, Warrington SJ, Gunn K, Cuddigan M, Turton DJ, Osman S, Frackowiak RSJ (1993) Dose dependent occupancy of central dopamine D₂ receptors by the novel neuroleptic CP-88,059-01: A study using positron emission tomography and ¹¹C-raclopride. *Psychopharmacology* **112**: 308-314.
- Bench CJ, Lammertsma AA, Grasby PM, Dolan RJ, Warrington SJ, Boyce M, Gunn KP, Brannick LY, Frackowiak RSJ (1996) The time course of binding to striatal dopamine D₂ receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by positron emission tomography. *Psychopharmacology* **124**: 141-147.
- Jones T (1996) The role of positron emission tomography within the spectrum of medical imaging. *Eur J Nucl Med* **23**: 207-211.
- Lammertsma AA (2004) Role of human and animal PET studies in drug development. *International Congress Series* **1265**: 3-11.
- Phelps ME (2004) PET: molecular imaging and its biological applications, Springer-Verlag, New York.

RATIONAL DESIGN OF LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTORS

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Nicotinic acetylcholine receptors (nAChRs) are members of the ligand-gated ion channel (LGIC) family that mediate and/or modulate synaptic signaling¹. They are members of the pharmaceutically important subfamily of pentameric ion channels, GABA_A, GABA_C, 5HT₃ serotonin, and glycine receptors. nAChRs play important roles in memory and learning processes and the absence of functional receptors is associated with multiple diseases including schizophrenia, Alzheimers disease, drug addiction and the autoimmune disease myasthenia gravis. nAChRs are the prime mediators of nicotine addiction in tobacco smokers. Because nAChRs have prominent roles in disease of the nervous system, they have become major targets in drug discovery programs.

nAChRs exist in subtypes with different physiological properties and pharmacology. The lack of detailed structural information about these receptors has hampered rational drug design. Structural information about the ligand-binding domains and the subunit interfaces has expanded upon discovery and crystallization of the water-soluble homologue of the ligand-binding domain of nicotinic receptors, the acetylcholine binding protein (AChBP)^{2,3}. The crystal structure of AChBP has become an established model for the extracellular domain of the pentameric LGICs and homology models have been generated to analyze receptor-ligand interactions. AChBP has pharmacological properties similar to the homomeric alpha-7 subtype of the nAChRs, with relatively weak affinity for acetylcholine and a 10-fold higher affinity for nicotine. The ligand binding site of AChBP is characterized by the presence of aromatic and hydrophobic residues that are contributed by two neighboring subunits. The recent crystal structures of AChBP⁴ in complex with nicotine and carbamylcholine have elucidated the molecular contacts between ligand and protein and are in excellent agreement with biochemical data obtained from nAChR binding studies. AChBP in complex with the nAChR agonists carbamylcholine and nicotine has revealed that both ligands bind at the same position and cause similar local conformational changes within the protein. These structures are useful tools for the development of new drugs for the nicotinic acetylcholine receptor and its family members.

References:

1. Wonnacott S, Sidhpura N, Balfour DJ. Nicotine: from molecular mechanisms to behaviour. *Curr Opin Pharmacol.* (2005) 5(1):53-9.
2. Smit AB, Syed NI, Schaap D, van Minnen J, Klumperman J, Kits KS, Lodder H, van der Schors RC, van Elk R, Sorgedraeger B, Brejc K, Sixma TK, Geraerts WP. A glia-derived acetylcholine-binding protein that modulates synaptic transmission. *Nature.* (2001) 411(6835):261-8.
3. Brejc K, van Dijk WJ, Klaassen RV, Schuurmans M, van Der Oost J, Smit AB, Sixma TK. Crystal structure of an ACh-binding protein reveals the ligand-binding domain of nicotinic receptors. *Nature.* (2001) 411(6835):269-76.
4. Celie PH, van Rossum-Fikkert SE, van Dijk WJ, Brejc K, Smit AB, Sixma TK. Nicotine and carbamylcholine binding to nicotinic acetylcholine receptors as studied in AChBP crystal structures. *Neuron.* (2004) 41(6):907-14.

FIRST PSYCHOTIC EPISODE: SYMPTOMS, CLASSIFICATION, TREATMENT AND BRAIN MORPHOLOGY

W. Cahn

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The word “psychosis” is used to describe conditions that affect the mind, in which there has been some loss of contact with reality. With an incidence of about 0.01% per year, the occurrence of a first psychotic illness is relatively rare, but the impact is devastating on the people that endure it as well as on their close relatives and friends. The trauma of suffering from a psychotic episode is expressed in the number of patients developing a post-traumatic stress disorder as a result (11 % of hospitalized patients). Patients with a first psychotic episode have to come to terms with suffering from a mental illness. Moreover, they have to learn to cope with the knowledge of the great risk of relapse after their initial recovery. Critical psychosocial influences, including family and psychological reactions to psychosis and psychiatric services, occur during the first psychotic episode. Therefore, important opportunities for secondary prevention arise during this period.

A psychotic episode can be caused by several psychiatric disorders including schizophrenia. Somatic disorders, like thyroid dysfunction and epilepsy, can also cause psychotic symptoms, as well as prescribed and non-prescribed drugs, alcohol or the withdrawal of these substances. Even though a careful assessment of the patient has been performed, it often remains difficult to diagnose the underlying psychiatric disorder. Several reasons can be contemplated to explain the diagnostic difficulties. Firstly, in first-episode psychosis the use of modern diagnostic systems (i.e. DSM IV¹) is restricted. Secondly, there is often a mixture of schizophrenic and affective features in the first psychotic episode, particularly in adolescent-onset psychoses.

Medication used in the treatment of a first psychotic episode varies and depends on the diagnosis. In schizophrenia antipsychotic medication is the treatment of choice. Antipsychotics have been found to shorten the length of the psychosis and to prevent relapse. In combination with medication, psychoeducation, cognitive therapy and rehabilitation have been found to improve clinical and functional outcome. However, even with optimal treatment, various patients continue to suffer from symptoms and their functioning is often impaired.

Since the early 90's a great deal of effort has been put in to develop research studies focusing on first-episode psychosis. Exclusion of prior treatment as a confounder is a great advantage for research in psychotic illnesses. Moreover, patients can be studied prospectively and treatment interventions can be evaluated that might influence the outcome.

In this lecture the symptomatology, differential diagnosis and treatment of a first-psychotic episode will be discussed. Longitudinal studies, in particular MRI studies investigating brain morphology, in the early stages of schizophrenia will be presented.

Reference

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. fourth edition (DSMIV) ed. Washington, DC: American Psychiatric Press; 1994.

ANTIPSYCHOTIC DRUGS: MECHANISMS OF ACTION AND PHARMACOLOGICAL PROFILES

T.R. Werkman

Center for Neuroscience, SILS, University of Amsterdam, t.r.werkman@uva.nl

In the 1950s the application of the first anti-psychotic drugs (APDs) like chlorpromazine meant an important breakthrough for the treatment of schizophrenia patients. Since then the search for better (i.e. effective against all schizophrenia symptoms and evoking less side effects) APDs has continued and with the marketing of new classes of APDs (including APDs like clozapine and aripiprazol) important steps forward in treating schizophrenia were made. However, at present the “ideal” APD still does not exist.

This lecture will address the pharmacology of APDs and how they are believed to interact with their targets in affected brain areas to yield an effective pharmacotherapy. All present APDs used in the clinic have in common that they are dopamine receptor antagonists. This property is an essential argument for the so-called dopamine theory, and confirms that disturbances in dopaminergic signaling processes in mesolimbic and mesocortical structures play an important role in the diverse symptoms observed in schizophrenia patients. In addition to dopamine receptor affinities, newer classes of APDs also interact with other neurotransmitter receptors (e.g. 5-HT₂ receptors). It will be discussed how the combined affinities for different neurotransmitter receptors are believed to render these drugs as better APDs. Finally some attention will be paid to drugs that are in the pipeline of R&D programs of many pharmaceutical companies and which do not interact with dopamine receptors (e.g. neurokinin receptors).

ANIMAL MODELS IN ANIPSYCHOTIC DRUG RESEARCH

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Animal models are experimental preparations developed in one species to study phenomena in other species (McKinney 1984). Although this implies that any animal species can model any other one, most animal models are designed to investigate human behaviour, or even more often human diseases. Animal models have been of great importance in investigating neurological and psychiatric diseases. This is primarily due to the limited accessibility of the human brain, in spite of new and advanced imaging techniques. Developing animal models for psychiatric diseases is hampered by two problems: 1. Most psychiatric symptoms are typically human, and can only be assessed by a clinical interview; 2. The aetiology and in most cases the neuropathology is virtually unknown, making it difficult to induce a similar disturbance in animals. However, it is increasingly realised that some of the symptoms as well as psychological and psychophysiological aspects of schizophrenia can also be measured in animals. Moreover, recent clinical research has provided evidence that schizophrenia results from a complex interaction between genetic, early and late environmental factors.

Although several different classes of animal models exist (Willner, 1993), we will limit the presentation to the class of the so-called simulation models. Using a structured approach the various techniques for developing and validating such simulation models for schizophrenia will be discussed showing the advantages and weaknesses of the current models. It will become clear that most animal models focus on either a genetic or an (early) environmental causal factor and relatively little attention has yet been paid to combining these two causal factors.

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GRAY AND WHITE MATTER DENSITY CHANGES IN SCHIZOPHRENIA

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Schizophrenia is a chronic psychiatric disorder affecting approximately 1% of populations around the world. Its symptoms include hallucinations, delusions, disorganized speech, disorganized behavior, abnormal or stereotyped movements, flattened affect, anhedonia, and cognitive impairments. In the majority of patients, schizophrenia is characterized by a progressive decline in emotional and social functioning. Although its cause is unknown, numerous findings from imaging studies strongly support the view that schizophrenia is a brain disease particularly involving decrements in gray matter. Global gray matter volume decreases of approximately 2% have been reported in schizophrenia. However, results from a recent meta-analysis of volumetric magnetic resonance imaging studies in schizophrenia also suggest that changes may be more prominent in some brain areas than others (Wright et al, 2000). However, diffuse gray (and white) matter abnormalities have also been suggested. Moreover, recent evidence suggests that the decreases in gray matter volume may be progressive over the course of the illness in schizophrenia (Mathalon et al, 2001). In a cross-sectional study we found that older patients with schizophrenia had proportionally more gray matter volume decrease as compared to younger patients (Hulshoff Pol, 2002).

Whether the excessive gray matter loss in schizophrenia affected the gray matter globally or whether some areas show more progressive decrease than other areas was not known. Therefore, we analyzed focal gray matter density across the 55-year time-span in these same 159 patients with schizophrenia and 158 healthy comparison subjects, using voxel-based morphology. A linear regression analysis was performed through all brains for each voxel separately, co-varying for sex, and handedness. The critical threshold t-value for a 2-tailed alpha significance level of $p < 0.05$ after correcting for multiple comparisons according to random field theory was $|t| > 5.0$. Its main finding was that distinct focal areas in the brains of patients with schizophrenia display decreased gray matter density, including the left amygdala; left hippocampus; right supramarginal gyrus; thalamus; (orbito) frontal, (superior) temporal, occipitotemporal, precuneus, posterior cingulate, and insular cortices bilaterally. Moreover, the decreased density in the left amygdala density was more pronounced in the older patients with schizophrenia (Hulshoff Pol et al, 2001). Since the amygdala has particularly widespread anatomical projections to the lateral orbitofrontal gyri and hippocampus – as well as to the medial orbitofrontal gyri, insula, temporal pole, and medial dorsal nucleus of the thalamus - while receiving extensive sensory input from the neocortex, our findings may suggest that a circuit involving the amygdala and its projection areas show (progressive) changes in schizophrenia. Involvement of the amygdala in schizophrenia would be consistent with its central role in emotional and social behavior, both of which are disturbed in schizophrenia. The amygdala represents an important route by which external stimuli can influence and activate emotions. It has been suggested that the amygdala enables the formation of stimulus-reward associations, and that these associations help to establish the emotional significance of external events, including social actions.

Whether these gray matter density decreases represent (an) aberrant neuronal network(s) in schizophrenia remains to be determined. White matter decreases of approximately 1 percent suggest that the fibers connecting the different areas may also be involved (Wright et al, 2000). Moreover, whether the excessive age-related decreases in the amygdala and connected brain structures are related to the genetic risk to develop schizophrenia or are related to (neurodegenerative) processes that are non-genetic in origin remains to be established in future studies. Smaller intracranial volumes in monozygotic patients and their cotwins suggested that increased genetic risk to develop schizophrenia is related to reduced brain growth early in life. Additional whole-brain volume loss was found in the patients, irrespective of zygosity, suggesting involvement of non-genetic processes

(Baare et al, 2001). Since gray matter volumes increase during childhood and then decrease before adulthood, with different areas changing at different rates per year (for review see Durston et al, 2001), involvement of developmental processes occurring during childhood may also be of influence on the (focal) changes in gray matter volume in schizophrenia.

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MULTIPLE SCLEROSIS PATHOGENESIS 2010: WHERE ARE WE NOW?

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system particularly affecting young adults. Neuropathological examination of brain tissue of individuals with MS demonstrates multiple lesions in the white matter. To date, evidence is accumulating that extensive demyelination also occurs in the cerebral cortex of chronic MS patients. Common pathological features of MS white matter plaques include blood-brain barrier leakage, destruction of myelin sheaths, oligodendrocyte damage and cell death, axonal damage and axonal loss, glial scar formation and the presence of inflammatory infiltrates that generally consist of lymphocytes and macrophages. In particular monocyte-derived macrophages contribute to MS lesion formation as they phagocytose myelin, which ultimately leads to damage of myelin sheaths and oligodendrocyte cell death. Importantly, during inflammation, macrophages secrete various inflammatory mediators, including cytokines, chemokines, nitric oxide, and reactive oxygen species, which all contribute to the progression of the disease. In spite of tremendous efforts the mechanisms underlying the pathogenesis of MS remain enigmatic. Although MS is traditionally considered as an inflammatory autoimmune demyelinating disease, recent findings have challenged this concept and evidence is emerging that degeneration of oligodendrocytes may be involved in the initial phase of the disease. Alternatively, recent findings point towards impaired mitochondrial function and primary axonal injury as main culprits. In this seminar I will discuss these pathological features underlying the formation and persistence of MS lesions.

THERAPEUTIC TARGETS FOR MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to severe neurological deficits. During autoimmune inflammation of the central nervous system (CNS), blood-derived immune cells cross the blood-brain barrier (BBB) to invade the CNS, and ultimately induce severe tissue damage. Normally the BBB protects the homeostasis of the CNS and the barrier actively hinders entry of serum proteins and immune cells into the brain by the presence of complex interendothelial tight junctions.

Under disease conditions such as multiple sclerosis, but also after a stroke or brain trauma, the BBB is disrupted leading to serum protein leakage. Immune cells attach to the activated brain endothelium through the interaction of adhesion molecules. Subsequent intracellular signalling cascades are responsible for opening of the tight junctions allowing leukocyte transmigration. After transmigration of the BBB, inflammatory cells accumulate in the perivascular space and traffic into the brain parenchyma, amplifying the inflammatory response and ultimately leading to brain tissue damage. Interference in the invasion process of tissue damaging immune cells is therefore a promising target for therapy. Based on basic research a number of novel drugs that interfere in the migration process are now under investigation for clinical use and pilot studies suggest a promising outcome, which will be discussed.

However, to block inflammation in the CNS, a high need for the identification of specific targets at the level of the neurovasculature is needed. Therefore, research on the development of therapeutic strategies to strengthen the BBB is of high importance and targets of interest will be discussed.

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MECHANISM-BASED PHARMACOKINETIC / PHARMACODYNAMIC (PK/PD) MODELING FOR CNS-ACTIVE DRUGS

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Our goal is to develop more mechanism-based PK/PD models to characterize and ultimately to predict CNS drug responses in both physiological and pathological conditions¹. To this end, it is essential to have information on the target site PK, because it may significantly differ from plasma PK². Target site kinetics of CNS drugs are in many cases strongly influenced by transport across the blood-brain barrier (BBB). BBB transport is related to BBB functionality which is the sum of passive diffusion and many active transport mechanisms, including for example the P-glycoprotein efflux transporter (Pgp). BBB functionality may vary among different physiological, pathological, as well as by chronic drug treatment conditions. It is anticipated that such variations in BBB functionality may affect the target site kinetics of CNS drugs and therewith the CNS effect-time profile of the drug². In vivo microdialysis enables the determination of free-drug concentrations as a function of time in extracellular fluid of the brain (brainECF), thereby providing important data to determine BBB transport characteristics of drugs. This is important for delineating the mechanisms that govern target site PK when combined with CNS effect measurements. In this presentation, 3 projects will be presented to illustrate the added value of mechanism-based PK/PD modeling of CNS active drugs.

* The role of the BBB in EEG effects of 7 opioids, showing that brain distribution of specifically morphine is determined limited passive diffusion; active efflux -partially reduced by Pgp inhibition-; and active uptake.

* L-DOPA BBB transport in the intracerebral unilateral rotenone model of Parkinson's Disease, showing that in diseased brain the basal concentrations as well as following L-DOPA administration, changes were found in kinetics of the dopamine metabolites, however, without concomitant changes in BBB transport of L-DOPA.

* The role of the site of administration (Intravenous vs intranasal) on remoxipride PK in brain and plasma and prolactin plasma concentrations, showing that differences in brain distribution of REM exist following IV and IN REM administration, with concomitant differences in PRL plasma concentrations.

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BIPOLAR DISORDER: AN INTRODUCTION TO MANIC-DEPRESSIVE ILLNESS

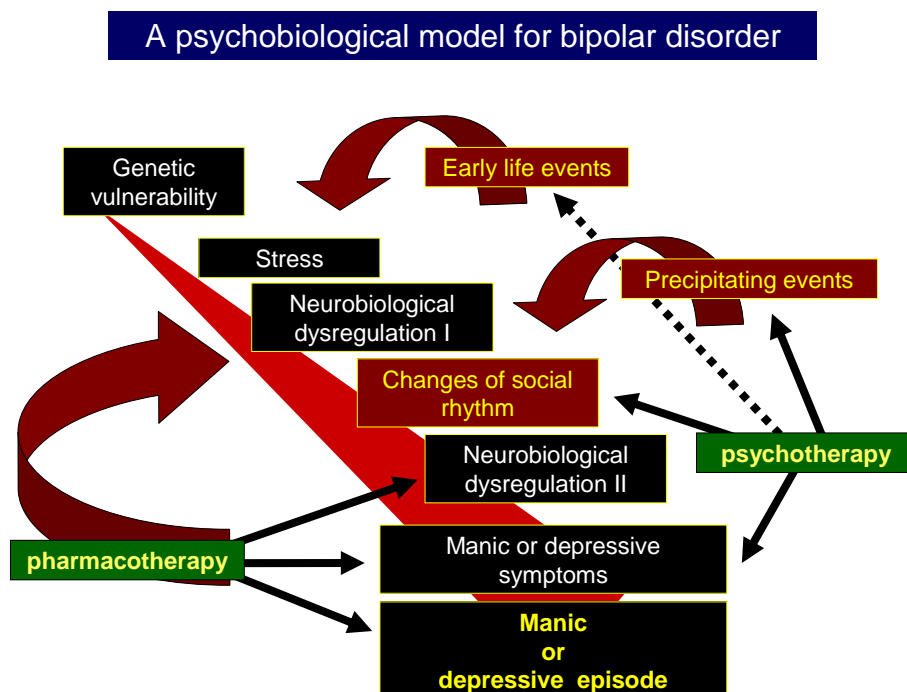
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Bipolar disorder (also called manic-depressive illness) is a severe and recurrent mood disorder characterized by the occurrence of episodes of depression, mania, and hypomania, in any give frequency and sequence. These mood episodes last form several days to many months, and are separated by symptom-free intervals that may also last up to many years. Illness episodes lead to severe functional impairment, and due to considerable behavioral disruption may have long-lasting consequences, especially in the areas of interpersonal relationships and work. Early diagnosis and treatment is therefore essential. Diagnosis of bipolar disorder is often delayed due to its heterogeneous symptomatology and course, and the differential diagnosis from unipolar depression, schizophrenic psychosis and severe personality disorder can be difficult.

Treatment of bipolar disorder is conceptualized in 3 phases, that often overlap in clinical practice: acute treatment, continuation treatment and prophylactic maintenance treatment. Acute treatment of bipolar depression, mania or mixed episodes is aimed at remission of symptoms. Continuation treatment of the index episode is aimed at prevention of relapse and ideally leads to symptomatic and functional recovery. Maintenance treatment is indicated when multiple episodes have occurred and is aimed at prevention of further episodes of at least diminishing their severity, duration, and consequences.

In this presentation an overview is given of the clinical presentations of bipolar disorder, its genetic and neurobiological background, and its treatment in various phases of the illness.



DEPRESSION: CLINICAL ASPECTS, PATHOGENESIS AND TREATMENT

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Mood disorders cover a wide spectrum of psychiatric illnesses, ranging from simple short non recurrent depressive episodes, to non recurrent long term episodes, to recurrent severe or even chronic episodes, to depressive episodes combined with hypomanic or manic episodes. The most simple classification is those with a unipolar (only depression) and those with a bipolar (depression and [hypo-]mania) course.

In this lecture the unipolar mood disorders or depression is the theme. We will describe the symptomatology, the different types, the different longitudinal courses and the overall prognosis. Predictors of chronicity and recurrency will be discussed.

The next subject will be pathogenesis in which we go to psychological and neurobiological points of view. Who is vulnerable for depression and why? What do we know about genetics so far? What neurobiological systems are involved?

Finally treatment in its different aspects will be discussed. What type of psychotherapies are known and what are their characteristics? What type of medications are used and how do we think they work? What is the role of electroconvulsive therapy (ECT), of transcranial magnetic stimulation (TMS) and what about deep brain stimulation (DBS)? Do we know the mechanisms of these treatments.

ANIMAL MODELS FOR DEPRESSION: OPPORTUNITIES AND LIMITATIONS

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Major depressive disorder is a common, devastating, chronic, and often life threatening disease. Treatment most times consists of cognitive behavioural therapy combined with drug treatment. Yet, despite years of research, there is still a large number of non-responders to drug treatment. Furthermore, currently available antidepressants have a delayed onset of action and several adverse effects. Hence there is a need for novel antidepressants with fast onset and better efficacy. For the development of novel antidepressants, compounds are tested in animal models for depression. Animal models are also used to study mechanisms involved in the pathophysiology of affective disorders. This latter line of research can help to discover novel drug targets for the treatment of depression.

Obviously an animal model can never replicate exactly the human disease state of depression. Willner (1984) therefore proposed three validities to determine the applicability of an animal model: Face validity, Predictive validity and Construct validity. Face validity refers to the accuracy with which the model reproduces the symptoms characterizing human depression. Construct validity evaluates the extent to which the etiology of depression is modeled. Predictive validity refers to the extent to which the effect of drug treatment in the model is predictive of effects in human depression. These three validities will be discussed, by showing several animal models of depression that are currently used in preclinical research. Furthermore, the limitations and opportunities that the various models hold for research will be discussed.

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NEUROPSYCHOPHARMACOLOGY OF TODAY'S AND FUTURE ANTIDEPRESSANTS

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Five main classes of antidepressant drugs have been or are in clinical use: monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors (NARIs), and mixed serotonin/noradrenaline reuptake inhibitors (SNRIs). Other antidepressant drugs also affect dopaminergic mechanisms, such as bupropion or act at specific GPCRs such as mirtazapine, being a 5-HT_{2A}/α_{2A} antagonists. A common theme is that all these drugs act on monoaminergic mechanisms. While antidepressant drugs show efficacy in the clinic, there remains a major unmet medical need, as antidepressant response rates are low, clinical improvement is delayed, and side effects remain an issue. In an attempt to find better antidepressant drugs, a variety of strategies have been employed in the past, including the use of combination therapies, drugs targeting novel mechanisms of action, e.g. related to glutamatergic mechanisms, neuropeptidergic mechanisms, or acting at intracellular signalling cascades. Pros and cons of these approaches will be discussed.

The second part of the lecture covers the field of mood stabilizers, such as lithium, and some of the molecular mechanisms through which these drugs may exert their effects. The utility of those mechanisms as targets for the development of novel antidepressant drugs will also be addressed.

IMAGING ANTIDEPRESSANTS: VISUALIZING MECHANISMS OF ACTION

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The introduction of antidepressant medication in the 1950s has greatly improved treatment options in major depressive disorder, and has stimulated extensive research. To date, a common mechanism of these drugs is stimulation of serotonergic and/or noradrenergic neurotransmission. While the current theory that posits that depression is caused by lowered serotonin and/or noradrenergic transmission is popular with therapists and patients alike, it is also an oversimplification.

Pharmacological mechanisms are not necessarily identical to pathogenetic mechanisms, moreover, antidepressant drugs are not effective in a considerable subgroup of patients.

Over the last two decades, neuroimaging techniques have greatly contributed to our understanding of neuropsychiatric disorders. With regard to depressive disorder, functional imaging studies have indicated an imbalance between hyperactive limbic regions coupled with hypoactive dorsal prefrontal areas, resulting in impaired emotion regulation as well as cognitive deficits. In this presentation, this will be illustrated using both SPECT ligand and fMRI data from our lab. In addition, the role of serotonergic dysregulation in the pathogenesis of depression will be discussed.

CNS DRUG DEVELOPMENT: FROM PHASES TO QUESTIONS

A.F. Cohen

New medicines are designed to bind to receptors or enzymes and are tested in animal cells, tissues and whole organisms in a highly scientific process. Subsequently they often are administered to human subjects with tolerability as the primary objective. The process of development is considered to be linear and consecutive, and passes through the famous four phases of development: phase I to explore pharmacokinetics and provide indications for safety and tolerability; phase II to examine the potential therapeutic efficacy of the compound in selected patients; phase III in which drug's efficacy and side effects are examined in large-scale clinical trials; and phase IV to monitor the drug during its clinical use in the target population. This is efficient for those projects where the uncertainty about the development is low. There is, however an increasing number of new prototypical compounds resulting from the increased biological knowledge with a high level of uncertainty. For these prototypical drugs development has to proceed in a much more adaptive manner, using tailor made objectives, development of special methodology and a cyclical rather than a linear type of project management. Development of such drugs should be aimed at answering specific questions about the investigational compound, rather than at performance of standard-type drug-studies. These questions systematically address issues like whether the drug penetrates the central nervous system, how it affects the target pharmacological mechanism, which relevant physiological effects it has, how the drug's characteristics are influenced by demographic variables, etc. This course will explore the different aspects of question-based development, and deal with the study designs, methodologies and analyses that can be used to provide the answers.

WHAT IS THE DOSE RANGE FOR FIRST-IN-HUMAN ADMINISTRATION?

J. van Gerven

Before a new drug is first administered in humans, a systematic process has been completed that starts with a range of preclinical *in vitro* and *in vivo* experiments to give confidence that the compound has the proper characteristics to be safely and effectively used in humans. *In vitro* assessment of the compound's binding affinity to a wide range of relevant pharmacological targets (receptors, enzymes, ion channels, *etc*) can provide indications for its selectivity. If the compound binds to a specific target, further studies can be performed to show how it affects the target pharmacologically (as an antagonist, inverse agonist, partial agonist, *etc*) and with which affinity and intrinsic efficacy. Large numbers of compounds can be screened for their proper pharmacokinetic properties, using a range of *ex vivo* models to predict gastrointestinal absorption, hepatic metabolism and blood brain barrier penetration. Eligible drugs can then be examined more integrally in different animal species, on how they are absorbed, distributed, metabolized and eliminated through and from the body and its different organs. This can be examined in great detail using radioactively labeled drugs, which allow tracing of the parent compound as well as its metabolites. Animal models can demonstrate at which concentrations the drug has pharmacological effects – both on physiological systems that are relevant for the drug's intended therapeutic use, and on systems that are important for safety and side effects. Disease models provide indications that these pharmacological effects can indeed be therapeutically relevant. Animals can also show the dose range that causes reversible and irreversible toxicological effects, after acute and long-term exposure. All these preclinical experiments provide information about the relationships between doses and concentrations of the investigational compound on the one hand, and its pharmacological, therapeutic and toxicological effect range on the other. Interspecies differences need to be carefully considered, particularly of the underlying pharmacological mechanisms in animals compared to humans. Usually, this requires the use of different animal models, and of translational paradigms like allometric interspecies scaling of pharmacokinetic characteristics and comparisons with meaningful positive controls. Based on a systematic assessment of all this information, the equivalent concentrations in humans are determined, and doses are predicted that are needed to reach safe and meaningful plasma levels in healthy volunteers (or sometimes patients). The most methodological approach is the determination of the Minimal Anticipated Biological Effect Level, which also takes potential species-related differences in pharmacological systems into account. This pharmacological MABEL-approach gradually replaces the traditional empirical approach, in which the No Adverse Effect Level (NOAEL – the highest dose level that produces no detrimental effects in the most sensitive species) is used as the basis for the first dose to be administered in humans. This lecture will give an overview of the information needed to determine the dose range for first-in-man-studies, show how this information can be integrated, and discuss some practical issues for new compounds with novel action mechanisms.

DOES THE DRUG ENTER THE CENTRAL NERVOUS SYSTEM?

Pharmacokinetics and pharmacodynamics of BBB-penetration

G.J. Groeneveld

The brain and spinal cord are separated from the blood by permeability barriers: the blood-brain barrier (BBB) and the blood-spinal cord barrier, respectively. The BBB protects the central nervous system (CNS) from exposure to potential circulating toxicants. The barrier is relatively poorly developed in some areas of the nervous system. This includes the area postrema, which is an important part of the vomiting system; and the spinal nerve entry zones and proximal nerve roots, which explains peripheral neuropathy is a frequent neurotoxicity. The BBB also influences the homeostatic, nutritive, and immune environments of the CNS and regulates the exchange of informational molecules between the CNS and blood.

The BBB consists of tight junctions of capillary endothelial cells and is further reinforced by degrading enzymes present in large numbers inside the cerebral endothelial cells and by a drug efflux-transporter system in the luminal membranes of the cerebral endothelial cells, which actively removes a broad range of drug molecules from the endothelial cell cytoplasm before they cross into the brain parenchyma.

Substances can cross the BBB by a variety of mechanisms including active -saturable- transport, transmembrane diffusion, adsorptive endocytosis, and extracellular pathways. Most drugs in clinical use to date are small, lipid soluble molecules that cross the BBB by transmembrane diffusion. Such molecules are poorly soluble in hydrophilic environments like blood and other extracellular fluids and urine. They are therefore highly bound to plasma proteins, and require metabolism to water-soluble products before they can be eliminated from the body. This complicates the pharmacokinetics of many traditional CNS-active drugs. The pharmacological requirements for BBB-penetrating drugs also limit the design of innovative drugs with novel targets within the nervous system. Therefore, many drug delivery strategies in development target peptides, regulatory proteins, oligonucleotides, glycoproteins, and enzymes for which transporters have been described in recent years.

In the development of a CNS drug it is of primary importance to first check whether a drug crosses the BBB and penetrates the CNS. This can be done invasively, e.g. through cerebrospinal fluid (CSF) sampling, realizing that CSF pharmacokinetics (PK) does not necessarily reflect brain tissue PK. Other possibilities are through scanning techniques such as positron emission tomography (PET), especially in case of receptor binding studies. Pharmacodynamic variables related to brain function also provide proof that the drug has entered the central nervous system, provided that the effects are relevant to the drug's pharmacological effects, and not explained by significant systemic disturbances.

Here, the physiology of the BBB, the implications for the pharmacokinetics and the pharmacodynamics of CNS drugs, and how to demonstrate BBB penetration of a drug will be discussed.

DOES THE DRUG HAVE ITS ANTICIPATED PHARMACOLOGICAL EFFECTS?

J. van Gerven

Drugs have a therapeutic effect because they influence a biochemical process, which corrects the pathophysiological derangement that underlies the disease. The same pharmacological effect can also influence biochemical processes at other sites, which are unrelated to the pathophysiology but lead to side effects. In addition, drugs that lack pharmacological specificity can affect other physiological processes. Many compounds also have pharmacologically active metabolites. The therapeutic window between the dose range that improves the symptoms and those that cause side effects is determined by the balance between all these desired and undesirable pharmacological activities, and by the way that physiological systems can compensate for their effects. Healthy subjects can only provide limited information about the effects of the drugs in patients, because the underlying physiology is altered by the disease. However, the pharmacological effects that are basic to a drug's clinical (therapeutic and adverse) effects can often be reliably assessed in healthy individuals. Moreover, the pharmacokinetic characteristics can also be determined in the normal population, if necessary supplemented with information from special populations like elderly subjects or renally or hepatically impaired patients. This information allows accurate predictions of the probable therapeutic range of a new drug, which can be used to optimize the dosing regimens for subsequent clinical trials in patients. Such trials address the important question how the pharmacological activity affects the disease process in patients. Therefore, it is important to characterize the pharmacological effects of a new drug in healthy subjects during early development. This is relatively straightforward for drugs that act in tissues that are easily accessible, like peripheral blood for immunologic agents or anticoagulants. Sometimes, peripheral blood forms a good representation of less accessible systems, such as the homology between serotonin reuptake transporters in thrombocytes and the brain. In many other cases, it can be quite difficult to directly demonstrate a drug's pharmacological activity, particularly in the central nervous system (CNS). PET studies can show whether a drug binds to its pharmacological target (usually a specific receptor, sometimes an ion channel or enzyme), and how this relates to doses or plasma concentrations. Such studies provide detailed information about the affinity of the drug to the target, but not about its efficacy after binding. A target-specific pharmacological effect can be demonstrated indirectly by showing that the drug has a dose-related physiological effect – provided that this effect is not caused indirectly by a remote effect in another system, like blood pressure reduction leading to EEG-changes, or nausea and vomiting causing elevations of neuroendocrine hormones. Many pharmacological mechanisms have well-established (although rarely unique) links to quantifiable physiological effects, such as temperature elevation and 5HT₂-stimulation, and prolactin release and D₂-inhibition. Such 'pharmacological biomarkers' lend themselves well for translational studies in animals, healthy subjects and patients. Such biomarkers are not available for many other and most new drugs, and different strategies must be applied to provide evidence that the drug has a pharmacological effect. These strategies range from 'demonstration of a signal' (meaning that any significant CNS-effect is interpreted as) to 'proof of pharmacological activity' (by showing that the CNS-effect is plausibly related to the drug's mechanism of action, and that the effects are closely related to the plasma concentrations). Different methods need to be employed to identify the pharmacological activity of modulatory drugs or silent (ant)agonists, which have no measureable effects on systems at rest (such as under normal conditions in healthy subjects). The current lecture will present different examples of how 'proof of pharmacological principle' can be demonstrated, using pharmacokinetic/pharmacodynamic modeling, pharmacological challenge tests, and comparisons of effect profiles with positive controls.

DOES THE DRUG HAVE MEANINGFUL (PATHO)PHYSIOLOGICAL EFFECTS?

Disease models and translational aspects

G.J. Groeneveld

For a drug to have a relevant therapeutic effect, a biochemical process must be influenced, which is related to the pathophysiological derangement that underlies a disease. Once a drug has been proven to exert the anticipated pharmacological effect that is expected to improve the disease, it is important to examine the physiological consequences of this pharmacological activity, as an intermediate step before pathophysiological processes are assessed in patients – and well before clinical effects are studied in clinical trials. Since drugs often affect different pharmacological targets, and each target can influence different physiological processes, it can be difficult to select the most relevant methodology. In drug development, measures of drug effects are called biomarkers. A biomarker is an indicator of a particular disease state or of a process related to the severity or presence of a disease state, which may be used to assess the effect of a drug. A good biomarker is related to the pathophysiology underlying a disease, and can predict when a certain effect is exerted by drug treatment, and what the extent of influence on the disease may be. If they reliably reflect clinical outcome, they are called surrogate endpoints, but this is the case for only very few biomarkers. There are relatively standard ways to measure a drug's adverse effects, also for CNS-active drugs, which often cause impairments of attention, cognition, visuomotor function, and a few other functional domains that are relatively easy to quantify. Such measurements provide important information about the side effect profile of a new drug and set an upper limit to tolerable drug levels. The side effect profile also gives a general indication of the neurophysiological systems that are affected (or spared) by the drug – which are often also relevant for the therapeutic effect; REM sleep reduction for instance is a side effect of antidepressants, but also a fairly reliable indication that a drug will improve mood. The selection of therapeutically relevant biomarkers is relatively straightforward for conditions with a well-understood etiology and a relatively simple pathophysiology, but this is rarely the case for CNS-diseases. Important information about potential biomarkers can be derived from animal models, which have been created to mimic human disease and to determine if a drug can alter symptoms or disease course. The predictive value of these models is strongly dependent on what is known about the pathophysiology of a disease, and will be low when a biochemical process hypothesized to be related to the pathophysiology is actually an epiphenomenon or caused by the pathophysiological state rather than a causative factor. Truly translational animal models are due to alterations, e.g. genetic or through pharmacological or behavioural manipulation, that can be applied in an identical fashion in animals as in humans, and which therefore have a strong predictive value. Most animal models are unifactorial, and therefore rather inaccurate indicators of the complex multifactorial cascading derangements that are involved in human diseases. Despite their limitations, animal models play an important role in early drug development, and can also be used to study a drug's effects on relevant human physiological processes – even though this only partly reduces the uncertainty about the drug's clinical efficacy. Many of the most useful models rely on behavioural or functional homologies between different animal species, including man. Anxiety, mood, cognition, and pain for instance are relatively preserved in evolution, although their expression should be viewed in the light of species-specific ethology. Anxiety, depression and pain for instance can be viewed as extremes of normal behaviour, and can be transiently evoked in animals and humans using comparable paradigms. Such human disease models are still relatively uncommon in drug development, although there is a large ongoing interest particularly in models of pain, stress or anxiety. More knowledge about the effect of a drug on the pathophysiology of a disease that is well-understood can also be gained by inducing a state resembling disease *ex vivo*, e.g. by exposing whole blood from animals, healthy subjects and patients to pathogenic factors. This presentation will explore some of the issues related to translation of drug effects throughout the different phases of drug development.

CLINICAL ASPECTS OF EPILEPSY

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Epilepsy is the most prevalent neurological disorder in humans. The incidence of epilepsy in Europe and North America is approximately 1% . The hallmark of epilepsy is the repetitive pattern of epileptic seizure recurrence. Epilepsy is therefore a generic term characterizing neurological disorders with the propensity to cause epileptic seizure occurrence rather than a single disease entity. The etiology of seizure disorders is therefore multifactorial since genetic, post-traumatic, post-infectious, metabolic, neoplastic or cerebrovascular diseases may all lead to the occurrence of seizures.

An epileptic seizure is caused by and often spontaneous, usually unpredictable and most commonly uncontrollable synchronization of large assemblies of cerebral neurons. Epileptic seizures are often recorded by means of the electroencephalographic (EEG) through amplification of synchronously occurring fluctuations in dendritic potentials. Pharmacological agents may exert their effect on either excitatory or inhibitory pathways thereby either facilitating or diminishing the chance of seizure occurrence. Similar effects may be obtained through applying electrical or magnetic stimulation to selected cerebrocortical structures.

Evidence at hand suggests that epilepsy exerts long-term deleterious effects on neurocognitive processing. Epidemiological evidence suggests that epilepsy is associated with an increased chance of mortality in addition to keep their real increased risk of bodily harm as a result of injuries sustained during seizures.

Investigations on epileptogenesis form the basis of our understanding of the complex homeostatic changes leading to the occurrence of seizures. A correct characterization of a seizure disorder is of crucial importance in the appropriate diagnosis and treatment of this condition. The international classification of epileptic seizures has come about thanks to long-term EEG/video monitoring by allowing common features of seizures to be described in characterized prior to their being brought in conjunction with specific epileptic syndromes. Adequate description of epileptic syndromes has in turn led to the development of rational therapy options for suppressing seizure occurrence. Present-day diagnosis of epilepsy makes use of various neurophysiological techniques, most notably of the EEG, in addition to advanced structural neuroimaging investigations, primarily Magnetic Resonance Imaging (MRI) and often of functional neuroimaging such as Positron Emission Tomography (PET) or Functional MRI (fMRI) scanning to better describe and define the tissue giving rise to seizures . Advances in three-dimensional multimodality matching of these techniques have been primarily driven by demand generated by the surgical treatment of epileptic disorders. This type of treatment which is reserved for a small percentage of patients suffering from severe and debilitating epileptic disorders aims at identifying and successfully removing the epileptogenic zone, i.e., the location and volume of tissue that has to be removed in order to render a patient seizure-free.

Current research in epilepsy aims at identifying specific biomarkers to better characterize epileptic syndromes. Unraveling the genetics of epilepsies and understanding the mechanisms leading to pharmacoresistance are two of the foremost challenges faced at the present time. Future rational interventions may involve development of therapies 'on demand' aimed at suppressing the occurrence of seizures.

PHARMACOLOGICAL MODULATION OF AMINOACID-RECEPTOR-MEDIATED SYNAPTIC TRANSMISSION

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Glutamate (Glu) and γ -aminobutyric acid (GABA) are the most abundant amino-acid synaptic transmitters in the brain and they play a central role in the regulation of many somatic and mental functions. With respect to epilepsy Glu-mediated excitation is involved in the initiation, maintenance and spread of epileptic activity, whereas GABAergic inhibition primarily acts to prevent, limit or terminate epileptic activity. Impairment of this inhibition invariably leads to excessive activation of excitatory neuronal circuits. Glutamatergic and GABAergic synaptic transmission are therefore important targets for anti-convulsant drugs. Surprisingly drug development has not yielded any drug that exclusively acts on the glutamatergic system. Therefore, this contribution deals primarily with the GABAergic system to discuss its role as a (potential) target for anti-convulsant, anti-epileptic or anti-epileptogenic drug therapy.

GABA is presynaptically formed through decarboxylation of glutamic acid. The release of GABA into the synaptic cleft primarily is a vesicular process, which is controlled by several presynaptic autoreceptors. Following its release in the synaptic cleft, GABA primarily activates postsynaptic receptors, but under excessive activity can also spill over to extrasynaptic receptors. Released GABA is subsequently taken up by the presynaptic nerve terminal or glial cells via reuptake transporters. Finally, GABA is catabolised by GABA transaminase to succinic semialdehyde.

The GABA_A-receptor is a chloride channel composed of various combinations of 5 subunits out of several classes of subunits (α 1-6, β 1-3, γ 1-3, δ , ϵ , π , θ , and ρ 1-3). In theory many subtypes of receptors are possible but in reality only a limited number occur in nature. The subunit composition of the receptor determines its pharmacological and electrophysiological properties. Different subtypes of receptors are also located in different regions and networks and are likely associated with different functions. Synaptic receptors have a more or less equal affinity for GABA, but extrasynaptic receptors are more sensitive. In contrast, classes of drugs (e.g. benzodiazepines, neurosteroids, barbiturates, anaesthetics, etc.) can differ considerably in their affinity for various subtypes of receptors.

GABAergic inhibition is a highly dynamic process and can adapt rapidly (in hours or even minutes) to changing conditions. For example, benzodiazepines can lose their efficacy after chronic use or in the event of status epilepticus. Adaptation can occur both pre- and postsynaptically. Assembly, membrane trafficking and receptor phosphorylation and degradation can quickly alter inhibition - and also responses to drugs - by changing subunit composition, receptor density and receptor properties.

In conclusion, many drugs have been developed that can suppress seizures by facilitating GABAergic inhibition, but they still lack the sensitivity and specificity to do this without considerable side effects.

STRATEGIES TO PREVENT OR STOP THE PROGRESSION OF EPILEPSY OR PHARMACORESISTANCE IN EPILEPSY

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Temporal lobe epilepsy (TLE) is one of the most frequent forms of epilepsy in adult epilepsy patients. There is strong evidence that it is originally generated by an initial insult, such as a status epilepticus, stroke, head trauma or long-lasting febrile seizures (Engel, 1996, Mathern, et al., 1996, Pitkanen and Sutula, 2002). After a latent period of several years, the epilepsy can develop and progress over time. A large percentage of TLE patients (with hippocampal sclerosis) is pharmacoresistant and can only be treated by surgical resection of the affected hippocampal region. The challenge is to develop drugs that could prevent the development of epilepsy in cases that there is a high risk of developing epilepsy. To this aim we need to get more insight into the mechanisms that play a role during epileptogenesis, the process by which the brain becomes epileptic. On the other hand we might also develop drugs that might help to overcome pharmacoresistance. In the presentation strategies will be discussed that are aimed at prevention of epilepsy or pharmacoresistance. These can vary from a strategy based to prevent inflammation or cell death, restoration of blood brain barrier or strengthening of inhibition.

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LOCAL DELIVERY AND CELL THERAPY FOR THE TREATMENT OF REFRACTORY EPILEPSY

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Systemic treatment with anti-epileptic drugs (AEDs) for suppression of epileptic seizures is often ineffective and approximately 30% of epilepsy patients suffer from uncontrolled seizures or unacceptable medication-related side effects. For those refractory patients it is important to search for innovative treatments. Local delivery of anti-epileptic compounds in epileptic brain regions may represent a promising treatment option with superior efficacy and reduced toxicity compared to the systemically administered AEDs. During this lecture a comprehensive overview of different local delivery strategies will be provided, ranging from pump-mediated delivery to cell-based delivery approaches. The scientific basis of these innovative strategies will be discussed and critically evaluated. At our laboratory (Ghent University, Belgium) experiments are performed on intrahippocampal delivery of adenosine in animal models of temporal lobe epilepsy. The results of these experiments will be presented and compared with available literature. Promising results have been obtained, although there remains a lot of debate about the most suitable approach, targets and time points for intervention. This lecture will conclude with suggestions for future research on local delivery for refractory epilepsy.

PHARMACOLOGY OF ION CHANNELS IN EPILEPSY

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The sodium current is the major determinant of the upstroke of the action potential and therefore one of the most important factors in determining cellular excitability. Not surprisingly many of the effective anti-epileptic drugs exert their main influence in one way or another on rather specific properties of the sodium channel. Most importantly they prevent high frequency firing by shifting the inactivation curve to lower potentials and lengthen the time constant for recovery from inactivation. In several animal models of epilepsy it was shown that the process of epileptogenesis is also accompanied by changes in rather specific properties of the sodium channels. However considerable differences in the observed effects might explain subtle differences in the severity of the epileptic phenomena that are observed. In classical kindling excitability is enhanced, but spontaneous seizures are rarely observed. This condition is characterized by a shift in inactivation function. The clinical effective dose of most of the anti-epileptic drugs reverses these shifts. In the status epilepticus model evoked by repetitive electrical stimulation, spontaneous seizures occur after a silent period of several weeks. In addition to the changes in inactivation function, this condition also involves a shift in the activation function. The explanation for these changes is not yet known, but there are indications that a shift in molecular composition of the sodium channel could be involved. Our current hypothesis is that such changes in particular if they occur locally and spatially restricted, lead to relative differences in sensitivity for anti-epileptic drugs, which would make control of the epilepsy extremely difficult.

HOW DOES THE BRAIN BECOME EPILEPTIC?

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Epilepsy is the third most common chronic brain disorder, and the most common one in children and young adults; still, our understanding of the basic mechanisms that generate spontaneous seizures is incomplete. A variety of epilepsies can arise from genetic causes, following acquired insults, and likely involve gene-environment interaction. The talk will discuss the clinical issues, and show how experimental approaches can be used to generate and mechanistic hypotheses and discover target molecules and pathways. These, in turn, are the basis of novel pharmacological therapies for epilepsy.

ADDICTION: NEW TREATMENT OPTIONS

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In this presentation I will start with a brief overview of the history of the concept of addiction starting with the moral model, followed by the pharmacological model, the symptomatic (psychodynamic) model, the disease model, the psychological (learning) model, and the social model. Based on these experiences, in the early 1980s the biopsychosocial model was introduced with dependence as the operationalisation of the integrated model. Since the early 1990s, the brain disease model has become the scientifically most dominant variation of the biopsychosocial model of addiction and neurobiology has become the most dominant research paradigm (Leshner, 1997; van den Brink, 2006).

In the second part of my presentation, I will give a summary of the brain disease model as we now understand it, including the role of genetic vulnerabilities and the ways that these vulnerabilities are translated into biological risk factors and changes in the brain following repeated exposure to addictive substances or rewarding behaviours. The main changes in the brain include the pre-morbid presence and worsening of reward deficiency as a consequence of repeated drug use, the development of salience, attentional bias and craving, and the pre-morbid lack and drug-related decrease of behavioural inhibition (Volkow et al., 2004; van den Brink, 2006).

In the third part of my presentation I will discuss existing and some novel pharmacological interventions based on the previously presented neurobiological model of addiction, including medications to reduce reward and salience, medication to reduce craving, medications to improve error monitoring and behavioural inhibition, and finally medications to replace illegal injectable drugs by legal and orally available substitutes (van den Brink & van Ree, 2003; Volkow et al., 2004).

In the fourth part of my presentation I will give a brief overview of the potential use of existing and new neurophysiological interventions in the treatment of addiction: neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS).

I will finish this presentation with some conclusions and recommendations for treatment and further research.

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KICKING THE HABIT-AUTOMATIC BEHAVIORS IN DRUG ADDICTION

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Drug addiction is a chronic relapsing brain disease characterized by a loss of control over drug intake. The descent from casual, recreational drug use to abuse, culminating in the compulsive patterns of drug taking that characterize addiction, is thought to be the result of drug-induced functional changes in the neural circuits involved in emotions (1), incentive motivation (2), habits (3) and the cognitive control over behavior (4). In my seminar, I will focus on the role of habitual behavior in drug addiction (5). I will discuss the hypothesis that over many occasions of drug use, the complex sets of behaviors associated with drug use become ingrained to such an extent that, when activated by drug-associated stimuli or exposure to the drug itself, the processes underlying drug seeking and taking are automatically engaged and very difficult to suppress, despite a conscious desire to abstain. The development of habitual drug use is thought to be the consequence of a shift in the striatal regions in control of drug seeking and taking, i.e. a progressive involvement of ventromedial (i.e. olfactory tubercle and nucleus accumbens shell) to dorsolateral striatal regions in drug use. I will therefore also discuss the recent evidence that dorsolateral striatal mechanisms play a particularly important role in the habitual aspects of drug use. Last, some remaining questions and caveats regarding to role of habits in addictive behavior will be discussed, as well as how changes in the neural circuits involved in emotions, incentive motivation and cognitive control over behavior interact with habit circuitry resulting in drug addiction.

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IMPULSIVITY AS A RISK FACTOR FOR ADDICTION

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Drug addiction and behavioral (non-chemical) addictions such as pathological gambling are frequently associated with disturbances in cognitive functioning. In particular, maladaptive levels of impulsive behavior are among the most prominent cognitive disturbances in drug addicts and pathological gamblers, and the behavioral expressions of impulsivity in addiction range from deficient inhibitory response control to impulsive decision-making. These maladaptive levels of impulsive behavior may result from prolonged drug exposure and have been proposed to play an important role in maintaining the compulsive nature of drug use [1]. Related to this, recent findings have demonstrated that impulsivity may also predispose individuals to become addicted [2,3], and this interrelationship between impulsivity and addiction is currently intensely studied. Thus, targeting impulsivity by means of pharmacological tools may provide a new approach for treating human addiction and – to date – preclinical models are best suited to unravel the neural correlates of impulsive behavior.

Over the last decades, several translational models measuring impulsivity in rodents have been developed and mainly have been adapted from human neuropsychological tasks. All of these models are based on principles of instrumental (operant) learning and use positive reinforcement, being mostly highly palatable food rewards, to shape and guide the animals' behavior. The most frequently used model to measure aspects of inhibitory response control in rodents is the 5-choice serial reaction time task, followed by the recently developed rodent version of the stop-signal task. In addition, delay of reinforcement procedures are the most prominent models used to measure impulsive decision-making (see for review of these models,[4]). Consistent with the therapeutic efficacy of amphetamine, atomoxetine and methylphenidate to reduce impulsivity clinically, these drugs have similar effects in the aforementioned rodent models of impulsive behavior and pharmacological studies over the last years have further identified and unraveled the role of various neurotransmitter systems in impulsivity [5].

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PREFRONTAL CORTEX PLASTICITY MECHANISMS IN HEROIN SEEKING AND RELAPSE

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Associative learning processes play an important role in relapse to heroin use. We show in a rat self-administration model that re-exposure to cues previously associated with heroin results in down-regulation of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate-acid receptor (AMPA-R) subunit GluR2 and a concomitant up-regulation of clathrin coat assembly protein AP-2 mu1 in synaptic membranes of the medial prefrontal cortex (mPFC). Reduced surface expression of AMPA-R was associated with decreases in AMPA/NMDA current ratios and an increase in rectification index in mPFC pyramidal neurons. Finally, systemic or ventral (but not dorsal) mPFC injections of a TAT-fused GluR2-derived peptide that interferes with clathrin-dependent GluR2 endocytosis, attenuated both rectification index and cue-induced relapse to heroin seeking, leaving sucrose seeking unaffected. Hence, we conclude that GluR2-R endocytosis and the resulting synaptic depression in ventral mPFC are critical for cue-induced relapse to heroin seeking. In addition to these effects on the glutamatergic system, heroin abstinence is associated with changes in the expression of extracellular matrix components surrounding GABAergic interneurons in the mPFC. Moreover, we observed increased inhibition of mPFC pyramidal neurons following cue-induced reinstatement, suggesting that adaptation of the ECM may augment responsiveness of GABAergic interneurons to heroin-associated stimuli. The identification of these cellular mechanisms may provide new avenues for developing pharmacological agents to prevent relapse to heroin use.

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Tripartite Synapses: astrocytes process and control synaptic information

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Astrocytes, a type of non neuronal cell, have been classically considered to play supportive roles for neurons, without being involved in brain information processing. However, during the last years evidence obtained by several groups has demonstrated the existence of bidirectional communication between neurons and astrocytes. Indeed, astrocytes respond to synaptic activity with intracellular Ca^{2+} elevations that can trigger the release of gliotransmitters that can influence neuronal excitability and synaptic transmission. These results have led to the establishment of the concept of the Tripartite Synapse, which represents a novel view of the synaptic physiology in which astrocytes exchange information with the neuronal synaptic elements. I will present data obtained in my laboratory at the Institute Cajal supporting this novel concept.

Our laboratory has focused on the study of the properties and mechanisms of the reciprocal communication between neurons and astrocytes. I will present results showing that astrocytes discriminate between the activity of different synapses and to integrate those inputs, due to the existence of cellular intrinsic properties, suggesting that astrocytes show integrative properties for synaptic information processing.

We are also interested in the consequences of the astrocyte activity on synaptic transmission. I will show that astrocytes can modulate action potential-evoked synaptic transmission at single hippocampal synapses. Ca^{2+} elevations in astrocytes transiently potentiate the probability of neurotransmitter release at single hippocampal synapses, through Ca^{2+} - and SNARE protein-dependent release of astrocytic glutamate that activates presynaptic metabotropic glutamate receptors. This transient potentiation of synaptic efficacy becomes persistent when neuronal and astrocyte activities are coincident, suggesting that astrocytes play an active role in the transfer and storage of synaptic information by the nervous system.

Finally, I will present data regarding the existence of endocannabinoid-mediated neuron-astrocyte communication and its physiological consequences on synaptic transmission, showing that astrocytes express functional type 1 cannabinoid receptors (CB1Rs) that upon activation by endocannabinoids released from pyramidal neurons increase the intracellular Ca^{2+} through $\text{G}_{q/11}$ - and phospholipase C-dependent release of Ca^{2+} from internal stores. This astrocyte Ca^{2+} signal evoked by endogenous stimuli (neuron-released endocannabinoids) evokes the release of glutamate, which activates NMDA receptors in adjacent postsynaptic neurons and potentiates synaptic transmission through activation of presynaptic metabotropic glutamate receptors.

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