UPMC Paris 6 - Master BI Neuroscience - UE 5BN17 - Année 2018-2019

Neuropharmacologie moléculaire : Structure, fonction et pharmacologie des récepteurs et transporteurs des neurotransmetteurs

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Lundi 07 janvier 2019

9h30 - 10h : **Laetitia Mony**
Présentation du module aux étudiants et distribution des articles à analyser

10h - 12h30 : **Jean-Philippe Pin, CNRS, IGF, Montpellier**
G protein coupled receptors (GPCRs ; 1st part)
Structure and activation mechanisms

14h - 16h30 : **Francine Acher, CNRS, Université Paris Descartes**
G protein coupled receptors (2nd part)
Modern tools for the development of new molecules acting on GPCRs: structure-activity relationship, molecular modeling, binding site modeling

Mardi 08 janvier 2019

9h30 - 12h : **Laetitia Mony, INSERM, ENS, Paris**
Ionotropic glutamate receptors
Molecular architecture, gating mechanisms and pharmacology. Targets of therapeutic interest in neurology and psychiatry

14h – 16h30 : **François Rassendren, CNRS, IGF, Montpellier**
P2X receptors : molecular physiology

Mercredi 09 janvier 2019

9h30 - 12h : **Pierre-Jean Corringer, CNRS, Institut Pasteur, Paris**
Pentameric ionotropic receptors (1st part)
Molecular organization and gating mechanisms. Clinical pharmacology and canalopathies associated with this class of receptors.

14h - 16h30 : **Alexandre Mourot, INSERM, Sorbonne Université (UPMC), Paris**
Optopharmacology : turning receptors into photoreceptors

Jeudi 10 janvier 2019

9h30 - 12h : **Nicolas Reyes, CNRS, Institut Pasteur, Paris**
Neurotransmitter transporters: structure, mechanisms and pharmacology

12h-17h: **Temps libre**
Préparation des présentations d'articles

Vendredi 11 janvier 2019

10h - 12h : **Isabel Lefevre, SANOFI, Chilly-Mazarin**
Design and development of a new drug: from an industry point of view

14h - 17h : **Présentation d'articles** par les étudiants en présence de quatre intervenants (Francine Acher, Pierre-Jean Corringer, Alexandre Mourot et Laetitia Mony)

Description and objectives

This module is about neurotransmitter receptors and transporters, which are key actors of neuronal communication. The recent boom in membrane protein structures sheds a new light on our understanding of the function and the regulation mechanisms of these proteins. It also provides an unprecedented structural and conceptual framework to discover and develop new molecules of pharmacological interest. This module will tackle the molecular and structural organization, as well as the operating mechanisms of the main classes of neurotransmitter receptors and transporters. We will present their activation principles, as well as their interactions with ligands. Emphasis will be put on the allosteric mechanisms and subsequent conformational dynamics. We will also show how malfunction of these proteins can be at the origin of pathologies, making them targets of therapeutic interest. Finally, using concrete cases, this module will introduce students to the development process of new molecules of neurological and psychiatric interest.

Prerequisite

Basic knowledge in protein biochemistry (amino acid properties, protein structure, ligand/protein interactions) and pharmacology (what is an agonist, antagonist; notions of competitive and non-competitive inhibition).

The following websites can be compulsed :
http://employees.csbsju.edu/hjakubowski/classes/ch331/protstructure/olprotein-aminoacid.html
http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/N/Noncovalent.html
http://www.wiley.com/legacy/college/boyer/0470003790/reviews/pH/ph_non-covalent.htm
http://euch3i.chem.emory.edu/supramolecular/noncovalent.html
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.section.285
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=genomes.box.5836
http://www.pdg.cnb.uam.es/cursos/Barcelona2002/pages/Farmac/Comput_Lab/Guia_Glaxo

Content

1 – G protein coupled receptors (GPCRs) (5h) – Following a general presentation of this very large receptor family, activation of metabotropic glutamate and GABA receptors will be studied in more details (agonist binding, signal transduction and G-protein activation), allowing identification of different pharmacological targets on these receptors (agonist binding site, transmembrane site, …). In addition, modern tools to design and develop new molecules acting on GPCRs will be presented (structure-activity relationship, molecular modeling, docking, pharmacophore modeling, high throughput screening of active molecules, …).

2 – Ionotropic glutamate receptors (iGluRs) (2h30) – The course will describe the diversity of iGluRs and the molecular determinants of the functional differences between the different iGluR classes. A focus will be put on the molecular mechanisms at the origin of receptor activation, desensitization and modulation. We will furthermore put an emphasis on the rich pharmacology of iGluRs, especially of NMDARs, and describe the therapeutic potential of the allosteric modulatory sites recently identified in AMPA and NMDA-type iGluRs.

3 – P2X receptors (2h30) - P2X receptors form the third major class of ionotropic receptors. The specificities (molecular architecture, gating, permeation…) of this class of ligand-gated channels will be presented at the molecular level. The functions and therapeutic potential of these receptors will also be addressed.

4 – Pentameric ionotropic receptors (2h30) – The presentation of the molecular organization of the receptors belonging to this family will highlight the similarities but also the divergences between the nicotinic and $5HT_3$ receptors (excitatory) and the $GABA_A$ and glycine receptors (inhibitory). We will analyze in more details the mechanisms of action of clinical drugs targeting these receptors (benzodiazepines, $GABA_A$ receptor allosteric modulators, $5HT_3$ receptor antagonists, …). We will also tackle the pathological consequences of numerous mutations affecting pentameric ionotropic receptors.

5 - Neurotransmitter transporters (2h30) – Major progress have been made in our understanding of the molecular mechanisms of neurotransmitter membrane transport. Atomic structures of neurotransmitter transporters and the mechanistic of these transporters (ionic gradient coupling, for instance) will be tackled. Being major targets of neuroactive compounds (antidepressants, psychostimulants), the structural basis of the action of these compounds on transporters will also be described.

6 – Optopharmacology (2h30) – This transversal course will describe photochemical and genetic strategies aimed at rendering neurotransmitter receptors light controllable, and provide an overview of the neurobiological insights gained from such approach.

7 – Finally, this course series will be concluded by a talk from a project leader in the pharmaceutical industry, who will present several aspects of the design and development of a new drug (2h).