Molecular Neuropharmacology :
Structure, fonction and pharmacology of neurotransmitter receptors
2021-2022

On site evaluations: 2h written exam + article presentation

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Courses will take place in room 305 in the 3rd floor of IBENS (46, rue d'Ulm 75005 Paris)

Monday, January 3th

9h30 - 10h: **Laetitia Mony**
Presentation of the course series and attribution of the articles to analyze

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

14h - 16h30 : **Laetitia Mony, INSERM, ENS, Paris**
Ionotropic glutamate receptors (Part I)
Molecular architecture, gating mechanisms and pharmacology. Targets of therapeutic interest in neurology and psychiatry

Tuesday, January 4th

9h30 - 12h : **Thomas Grutter, CNRS, Faculté de pharmacie, Strasbourg**
Pentameric (1st part) and trimeric ionotropic receptors
Molecular organization, allosteric regulation and gating mechanisms

14h – 16h30 : **Pierre-Jean Corringer, CNRS, Institut Pasteur, Paris**
Pentameric ionotropic receptors (2nd part)
Clinical pharmacology and canalopathies associated with this class of receptors.

Wednesday, January 5th

9h30 - 12h : **Alexandre Mourot, INSERM, Sorbonne Université, Paris**
Optopharmacology: tuning receptors into photoreceptors

14h - 16h30 : **Jonathan Elegheert, CNRS, IINS, Bordeaux**
Ionotropic glutamate receptors (Part II)
Molecular interactions, non-ionotropic signaling mechanisms, recruitment and integration into the synapse

Thursday, January 6th

9h30 - 12h : **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

14h-16h: **Free afternoon. Q & A session.**

Friday, January 7th

10h - 12h : **Isabel Lefevre, SANOFI, Chilly-Mazarin**

Design and development of a new drug: from an industry point of view

14h - 17h30 : **Article presentation** by the students

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) (5h) – The first 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. The second course will focus on non ionotropic signaling and on the molecular interactions tetrameric receptors make with pre and post-synaptic elements of the synapse.

4 – Pentameric ionotropic receptors (5h) – 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 – 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.

6 – 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).