Drug Actions on the Nervous System

Biology 338

Prof. Nancy Kleckner Office: 312 Carnegie
Email: nkleckne@bates.edu Phone: 207-786-8201

ABOUT THE COURSE:

The specific ways in which most drugs interact with the nervous system are not completely understood. Many of the drugs that we do understand seem to interact with a limited number of sites within the nervous system, and these sites are often located at synapses. In order to understand how drugs work, therefore, we must understand the synapses they interact with. This course begins with the general principles of pharmacology and drug access to the nervous system, and then describes the basics of neuronal signaling, focusing on synaptic transmission. Individual neurotransmitter systems are then studied, along with the drugs and diseases that are associated with them. Students design the last section of the course, which focuses on nervous system function and dysfunction and the drugs and other therapies used for those dysfunctions. The specific objectives of the course are listed below.

Objectives:

1) The first part of the course is designed to allow you to understand how signals cross neuronal synapses and how drugs enter the nervous system and interact dynamically with receptors and other neural proteins.

2) The second part of the course is designed to investigate individual neurotransmitter systems and the drugs that interact with them. Here students learn the nuts and bolts (well, proteins and chemicals, actually) of each specific type of synapse and the most likely drug targets of each.

3) Another objective of this course, and of the third section in particular, is to facilitate student participation in their own learning, while at the same time taking into consideration the larger question: How do these drugs, through their cellular mechanisms, affect neural systems and behavior? Students present material of their choosing in discussion and lecture format. The final project assignment lists a number of topics for students to choose from. Students are expected to choose a topic of interest that they are **not** familiar with to maximize their learning.

4) A final objective is to give students the opportunity to look at the scientific literature with a critical eye. Much of what you read in the scientific literature is probably true, but you have undoubtedly heard the expression that you cannot believe everything you hear. This is also true when reading papers from the scientific community (scientists are human, after all). Students learn to critically analyze, and evaluate in writing, articles from the primary literature.

What you are expected to know upon entering this course:

You are expected to know some basic cell biology, including how membrane potentials are generated and maintained, and how action potentials are generated. You should also have a general knowledge of how neurons communicate with one another at the synapse, although this will be reviewed in detail. You can review all of this information in a Bio s42 text, such as Lodish's Molecular Cell Biology, or Albert's Essential Cell Biology. Please do so before the second day of class if you do not feel comfortable with this material. The material in the NS/PY 200 text is too simplified and inaccurate for this purpose.

Additional expectations:

Students are expected to come to all class meetings prepared to discuss the readings for the day. All assignments will be given in writing and are to be turned in on or before the due date. Exceptions are granted only in advance and in person (except when Dean's excuses are obtained). Your instructor will attempt to return graded assignments promptly when turned in on time.

READINGS:

Text: (required)

Nestler, E.J., Hyman, S.E., Malenka, R.C. Molecular Neuropharmacology, A Foundation for Clinical Neuroscience, McGraw-Hill, New York, 2001.

This is a good book for basic information about neural signaling, as well as information about drug actions in the central nervous system, with less coverage of the peripheral nervous system. It gives very good descriptions of neurotransmitter systems followed by descriptions of the drugs that interact with these systems. The last part of the book focuses on drugs involved with specific functions and disorders.

Other Books on Reserve at Ladd Library:

Cooper, J.R., Bloom, F.E., and Roth, R.H. The Biochemical Basis of Neuropharmacology, Oxford University Press, New York, 1996.

This text has the best description I have found of the nature of the synapse with reference to sites of action for drugs. However, it is not the easiest of books to read.

Nicholls, D.G. Proteins, Transmitters and Synapses, Blackwell Science Ltd, Cambridge, MA, 1994

This book is old, but provides a description and *wonderful* diagrams of the components of synapses. It is great for detailed information on synapses and neurotransmitter systems that are not described in other books.

Julien, R.M. A Primer of Drug Action, W. H. Freeman and Company, New York, 1998.

This text contains information about the types and actions of drugs that act within the central nervous system, and will be useful primarily in the last part of the course. Unfortunately, it lacks information about the peripheral nervous system.

Robbers, J.E., Tyler, V.E. Tyler's Herbs of Choice, Haworth Herbal Press, New York, 1999.

This text is an excellent resource for the mid-semester herbal supplement project, and you might want to buy it if you have an interest in herbal and alternative medicines (see amazon.com or local bookseller). It is on reserve in the library, and several other books with similar coverage are available in the book stacks.

Reserve Articles:

Additional required readings, consisting of review articles and primary articles, will be placed on 2 hour reserve in Ladd Library. These are referred to by number (R1, R2, etc.) in the schedule, and the full citations are given below. The list is not complete. Full citations for other articles will be provided once papers are chosen.

R1: Clark, W.G, Brater, D.C., and Johnson, A.R. Drug Receptor Interactions, *In*, Goth's Medical Pharmacology, 13th edition. Mosby Year book, St. Louis, 1992, pp. 6-12.

R2: Pardridge, W. M. CNS drug design based on principles of blood-brain barrier transport, J. Neurochem. 70: 1781-1792 (1998).

R3: Hubbell, J.A., Enhancing drug function, Science 300: 595-596 (2003).

R4: Brown, R.C. et al., Protection against hypoxia-induced increase in blood-brain barrier permeability: role of tight junction proteins and NFκB, J. Cell Sci. 116: 693-700 (2003).

R5: Schreiner, M. Paediatric clinical trials: redressing the imbalance, Nature Reviews 2: 949-961 (2003).

R6: Frantz, S., Antidepressant use in children questioned, Nature Reviews 2: 939 (2003).

SCHEDULE:

Section I - Basic Principles of Neuropharmacology			
Week	**Date**	**Topic**	**Reading**
1		Course Introduction Drug-receptor interactions	NHM 1
		Drug receptor interactions	NHM 1 R1
2		Introduction to neurons and glia	NHM 2
		Glial cells and the blood brain barrier	R2, R3, R4
3		Electrical excitability and ion channels **Summary of R4 due**	NHM 3
		Principles of synaptic transmission	NHM 4
4		Signal transduction pathways	NHM 5, 6
		Review of basic principles of neuropharmacology **Hand out take-home exam I**	
5		Excitatory and inhibitory amino acids **Critique of R4 due**	NHM 7
		Modulation of amino acid receptors **Take-home exam I due**	
		WINTER BREAK	
6		The catecholamines	NHM 8
		Serotonin Depression and clinical trials in children	NHM 9 R5, R6
7		Acetylcholine and the neuromuscular junction	NHM 9, TBA
		Neuropeptides and purines	NHM 10, TBA
8		**Supplement Presentations**	

		Project summaries due	
		Neurotrophic factors **Hand out take-home exam II**	NHM 11, TBA
Section III – Neuropharmacology of Specific Neural Functions and Related Disorders			
9		Topic to be announced	TBA
		Topic to be announced **Take-home exam II due**	TBA
10		Final project presentation	TBA
		Final project presentation **Second critique due**	TBA
11		Final project presentation	TBA
		Final project presentation	TBA
12		Final project presentation	TBA
		Final project presentation **Critique on your paper due 4 pm Friday, April 9** **Hand out Final Exam**	TBA
Finals Week		**Final Exam Due**	

GRADING:

The grades will be based upon performance on exams (at least two, the first and last take-home exams), 1 - 3 literature critiques (graded on understanding of science, critical ability, and quality of writing,), 1 or 2 presentations (supplement project and/or final project; graded on thoroughness, style of presentation, ability to stimulate discussion and written summary), and participation in classroom discussions.

The grade breakdown and assignment weights are flexible. You must take the first exam and the final; you must write the first summary and critique; you must do at least one of the two presentations; the participation grade is mandatory. The other assignments are optional, as long as your assignment weights add up to at least 90 %. If your weights do not add up to 100 %, each of the individual assignment weights will be increased (for example by 10 % if you only do 90%). This allows you some choice of assignment formats to accommodate individual learning styles. See table below:

Table of assignment weights	Percent of grade (based on 100 %)	Required assignments
Exams		

I (take-home)	20 %	20 %
II (take home)	20 %	
III (final, take-home)	20 %	20 %
Literature critiques		
I (instructor choice)	15 % (may rewrite)	One required at 15 %
II (student choice)	15 %	
III (final project paper)	15 %	
Supplement Project		
Presentation	10 %	One required at 15 %
Summary	5 %	
Final Project		
Presentation	10 %	
Summary	5 %	
Participation	10 %	10 %
Total	90 – 145 %	80 % required items. Must accumulate 90 % minimum