



Trip Report for
**“ACS Short Course: Essentials of Medicinal Chemistry
and Pharmacology”**
New Brunswick, New Jersey
June 27-28, 2007

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Abstract: *This ACS Short Course was intended for chemical scientists who have little or no formal training in physiology, pharmacology, or medicinal chemistry. The Course reviewed key concepts including modern drug concepts of drug action, drug-receptor interactions, pharmacophore analysis, concepts of PK and PD, drug efficacy and potency, and modern drug design approaches including structure-based and ligand-based drug design.*

*Speaker: J. Phillip Bowen
(Center for Drug Discovery, Department of Chemistry and Biochemistry),
University of North Carolina at Greensboro.*

The following course objectives were set forth:

- Discuss some of the fundamental principles and concepts that serve as a basis for understanding medicinal chemistry and pharmacology.
- Review background material that might be most helpful to chemists and pharmacologists.
- Show the important roles chemistry, physics and biology play in understanding pharmacology and medicinal chemistry concepts.
- Emphasis placed on understanding drug design concepts.
- Introductory course.

The course was broadly divided into the following sections:

- Review of fundamental concepts.
- Introduction to Drug Action: Pharmacodynamics.
- ADME/Tox: Pharmacokinetics.
- Pharmacophore development.
- Peripheral Nervous System.
- Enzyme inhibitors.
- QSAR, Computational Chemistry and Computer-Assisted Drug Design (only very briefly touched upon due to lack of time).

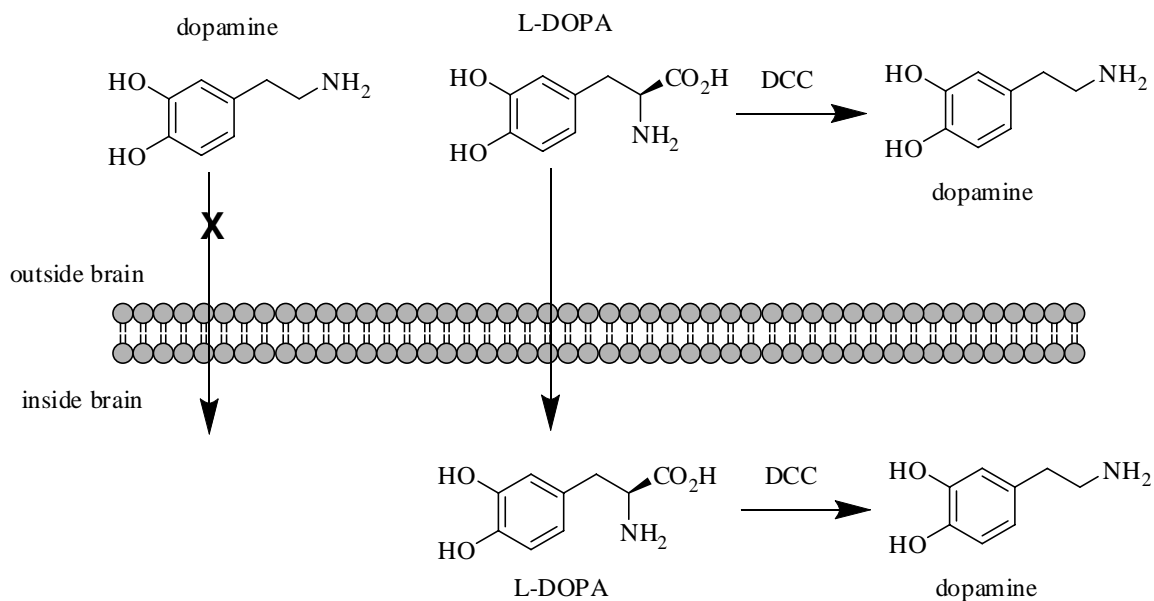
Some selected examples from the course are detailed below.

Blood Brain Barrier (BBB) and the treatment of Parkinson's Disease

An introduction to the BBB was included in the course, explaining that the Central Nervous System (CNS) is not easily penetrated by most substances, in part due to the CNS blood capillaries having an extra fatty layer present and having no (wide) pores. The potential treatment of Parkinson's Disease, a disease characterized by low levels of the neurotransmitter dopamine in the brain, and the relevance to the BBB was discussed.

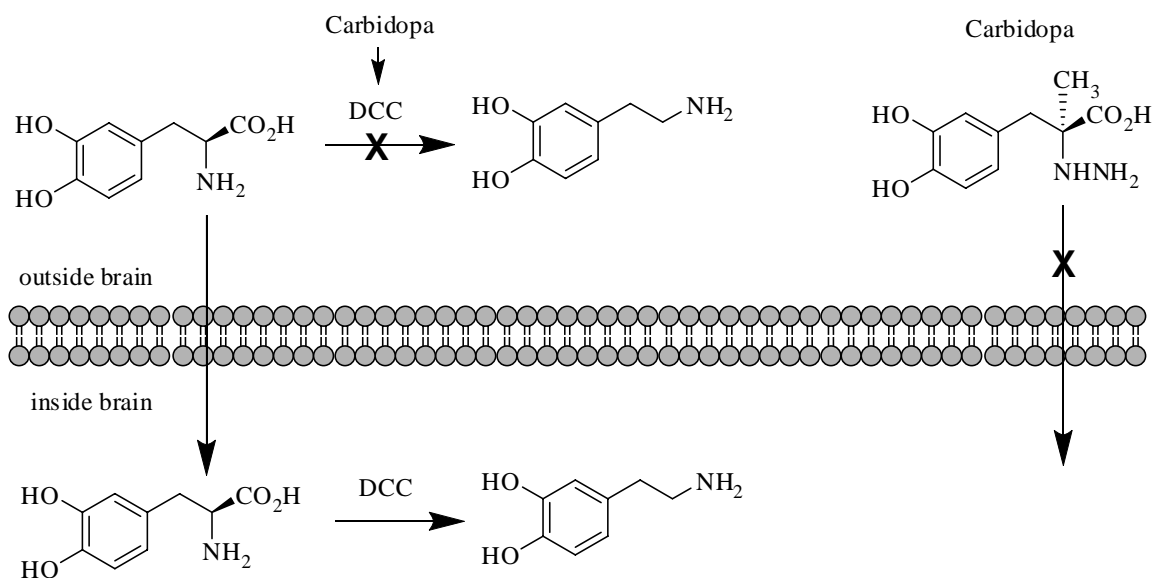
Orally administered dopamine is unable to cross the BBB and hence unable to treat Parkinson's Disease. L-DOPA is actively transported across the BBB and then is decarboxylated by aromatic-L-amino acid decarboxylase (Dopa decarboxylase or DDC) to provide dopamine in the brain (Figure 1).

Figure 1



Unfortunately, aromatic-L-amino acid decarboxylase also exists in the periphery where it can decarboxylate L-DOPA before it has a chance to cross the BBB. This excess peripheral dopamine causes undesired side-effects such as drowsiness. Administering L-Dopa along with Carbidopa, an aromatic-L-amino acid decarboxylase inhibitor, increases the plasma half life of L-DOPA from 50 minutes to 1.5 hours and allows more L-DOPA to be transported into the brain (Figure 2). Crucially, Carbidopa is not able to cross the BBB and thus cannot inhibit conversion of L-DOPA to dopamine inside the brain.

Figure 2



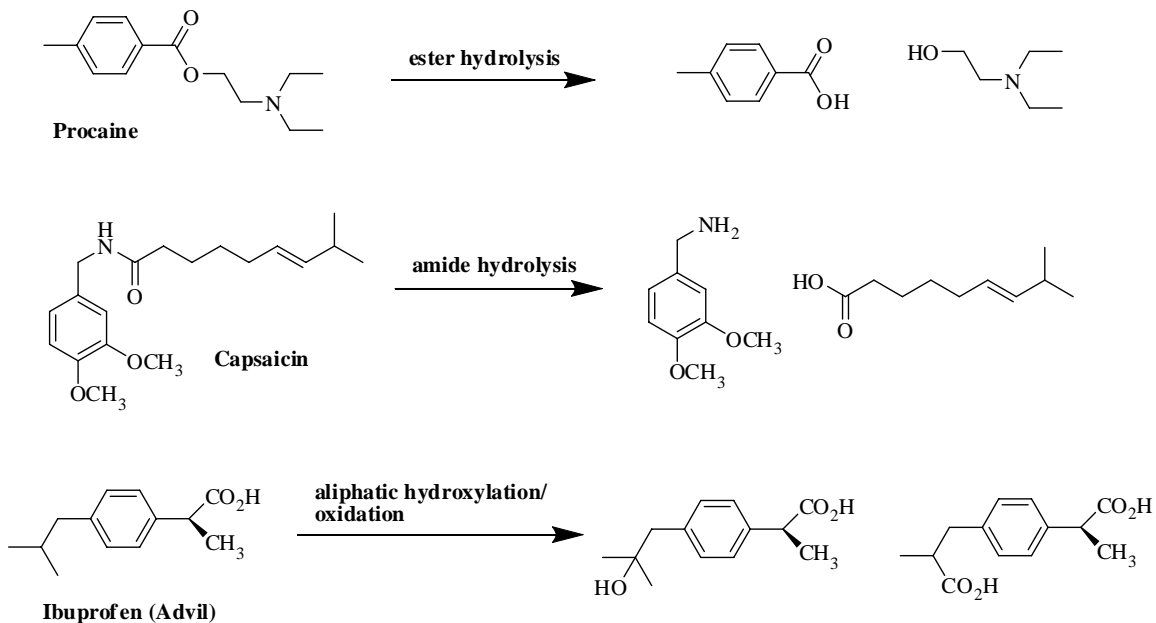
Introduction to ADMET; Concept and Considerations

Some important ADMET quotes:

- “Poor absorption and related poor pharmacokinetics is one of the main reasons for attrition in the drug development process.”
- “It is now widely recognized that physiochemical, pharmacokinetic, and biopharmaceutical properties need to be addressed early in the drug discovery.”
- “...surveys suggest that about 50% of all potentially therapeutic compounds undergo attrition due to safety concerns and that about 50% of them already had some indication in the literature already.”

Basic ADMET considerations were discussed including routes of administration (oral, sublingual (under the tongue), buccal (cheek), Nasal, Ocular, injections, rectal, transdermal, topical) and routes of elimination; urine, feces, respiration, perspiration, breast milk, saliva, regurgitation) followed by Lipinski's rules. Phase I and Phase II metabolism was briefly discussed with some examples given below (Figure 3).

Figure 3



Summary

The course was ideally suited to those with little or no medicinal chemistry knowledge (in my opinion). The presenter covered a wide range of medicinal chemistry topics, and in most cases highlighted the key points without going into too much detail for a beginner course. I would recommend the course for newly hired AMRI Senior Research Scientists that have had minimal exposure to medicinal chemistry and pharmacology and who are interested in learning more about the topic.