In vitro models for the determination of drug mode of action

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Our service offering includes several models for the identification of the molecular targets of a drug and of its off-target effects

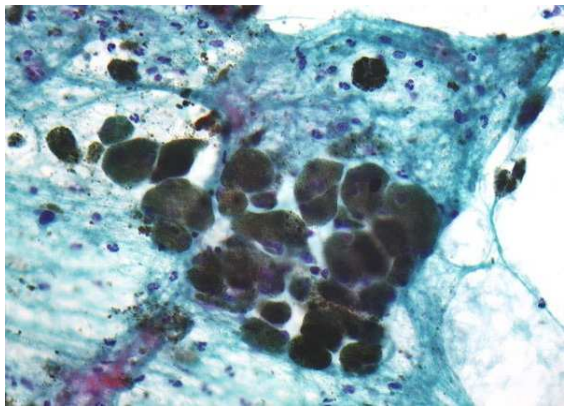
Melanin binding of drugs

It has been shown that melanin a pigment found in the skin and other parts of the body has an ability to bind drugs. Drug binding to melanin is causative for a multitude of physiological, pathophysiological or toxic effects in biological systems.

Presence of melanin in the human body

Melanin-containing tissues have been located in various parts of the human body:

- skin
- hair
- eye
- heart
- lungs
- liver
- inner ear
- brain substantia nigra (neuromelanin)



Melanin has a multitude of physiological functions dependent on the tissue:

- protection from UV light
- sequestering of harmful substances (organic compounds, heavy metals)
- redoxpolymer

A contribution of drug-melanin binding is established in several disorders:

- pigment disturbances of skin and hair
- ocular toxicity
- chorioretinopathy
- macular degeneration
- ocular phototoxicity
- ototoxicity
- M. Parkinson
- extrapyramidal symptoms
- carcinogenicity of drugs
- several forms of cancer (malignant melanoma)

Melanin binding also may influence drug delivery in pigmented tissues.

Examples of drugs accumulating in melanin

- β-adrenergics (propranolol, metoprolol, timolol, clenbuterol)
- antimalarials (chloroquine)
- neuroleptics (haloperidol, risperidone)
- antibiotics (amikacin, tobramycin)
- benzodiazepines (flunitrazepam)
- carcinogenes (benzopyrene)
- nicotine and its combustion products
- metal ions: iron, copper, lead, nickel

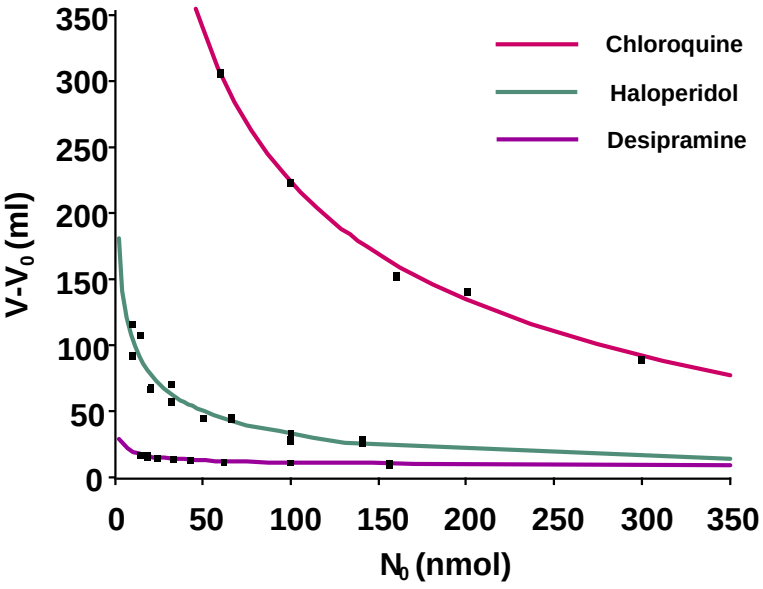
Determination of drug-melanin interaction

IBAM offers a self developed and patented assay based on affinity chromatography for the determination of melanin affinities of drugs.

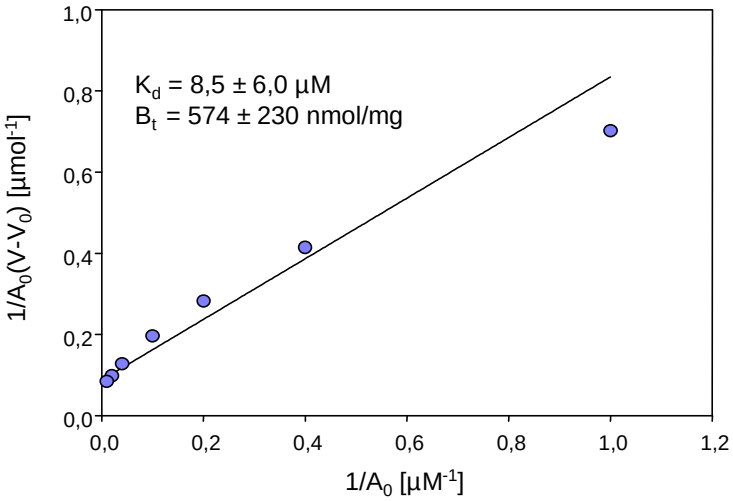
The advantages of this affinity chromatographic approach are:

- dynamic model: binding to and displacement from melanin can be studied
- use of native instead of radiolabelled substances
- competing binding studies of two or more drugs to melanin are possible.

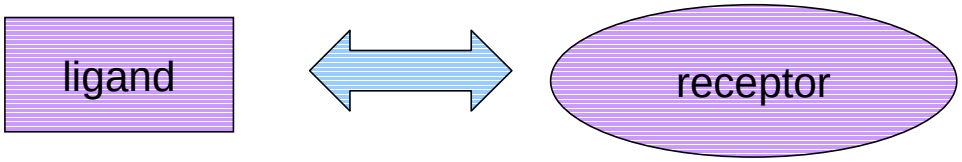
The study of drug-drug interactions is of foremost importance in drug safety. Displacement of one drug by another from its binding sites on melanin provokes an increase in the free concentration of the drug with sometimes grave toxicological consequences.



Binding of the antimalarial drug chloroquine to melanin examined by frontal affinity chromatography

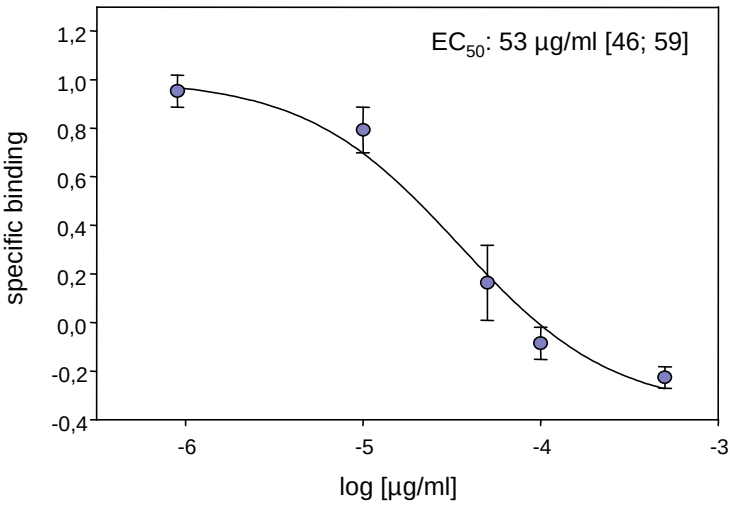


Receptor binding assays

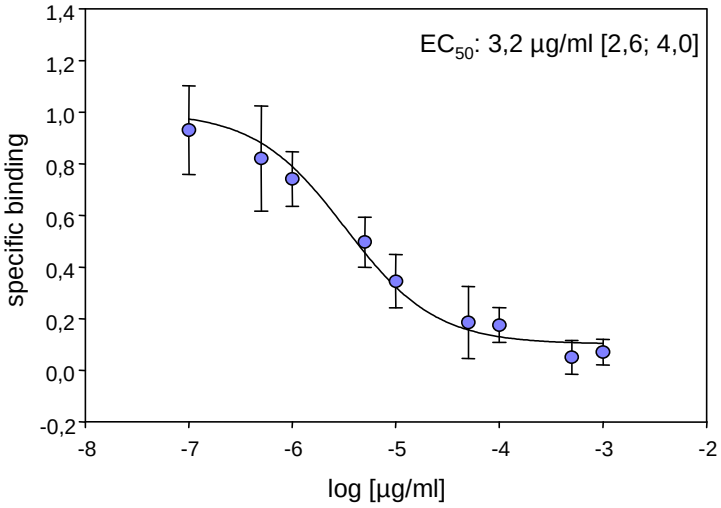


We offer a characterisation of the pharmacological profiles of drugs.
Based on this knowledge, drug effects may be explained and new indications for the drugs may be found.

Binding of a *Sideritis scardica* DMSO extract
to recombinant human α_2 receptors

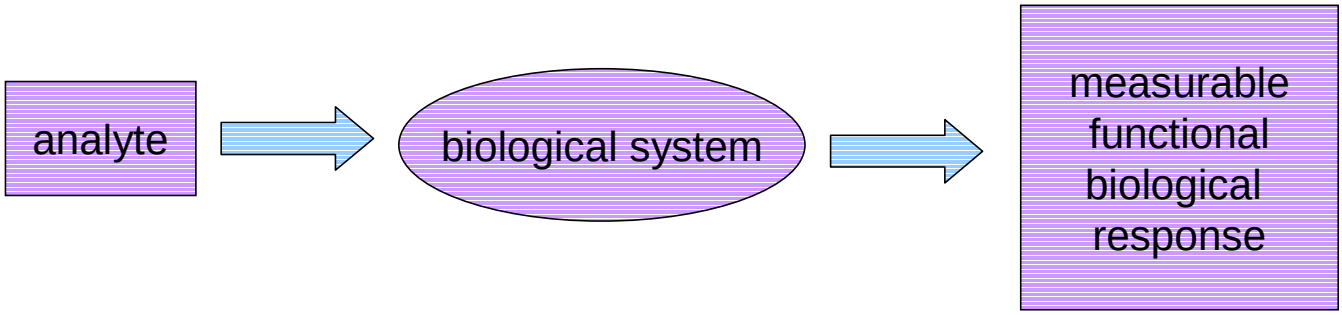


Binding of a plant extract
to recombinant human MT_1 receptors



Functional assays

Binding of a ligand to a receptor does not necessarily induce a biological response. Therefore, we offer multiple target functional bioassays using isolated organs, intact cells or cell preparations.

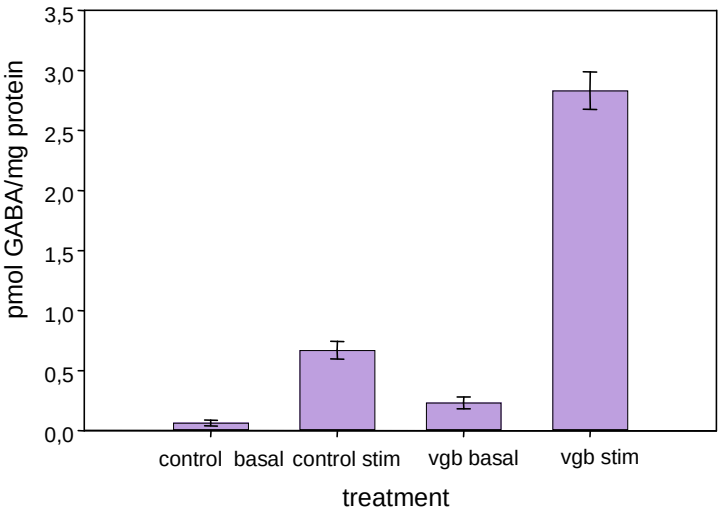


Release and uptake experiments

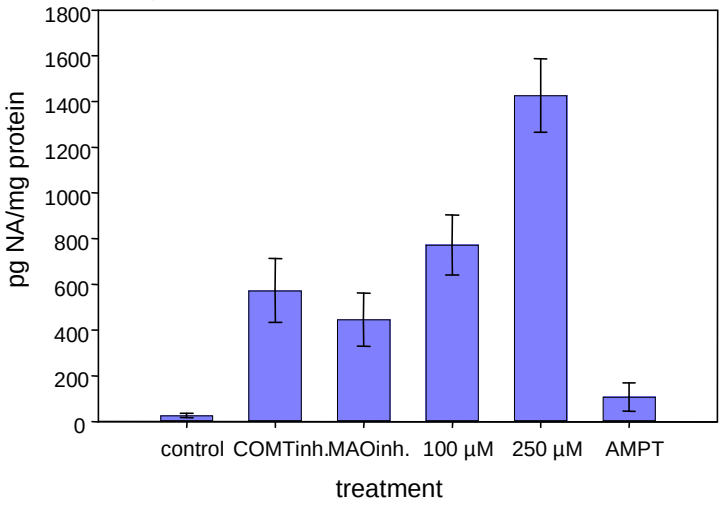
We provide several models to study drug-induced modulation of neurotransmitter and hormone release
(amino acids, catecholamines and their metabolites, biogenic amines).

Experiments can be performed with tissue slices, synaptosomes and cell lines.

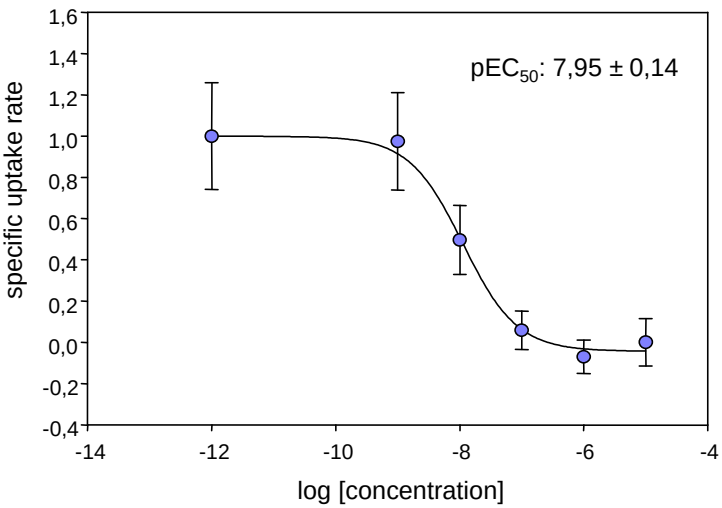
Effect of the GABA-transaminase inhibitor vigabatrin
on the extracellular GABA concentration



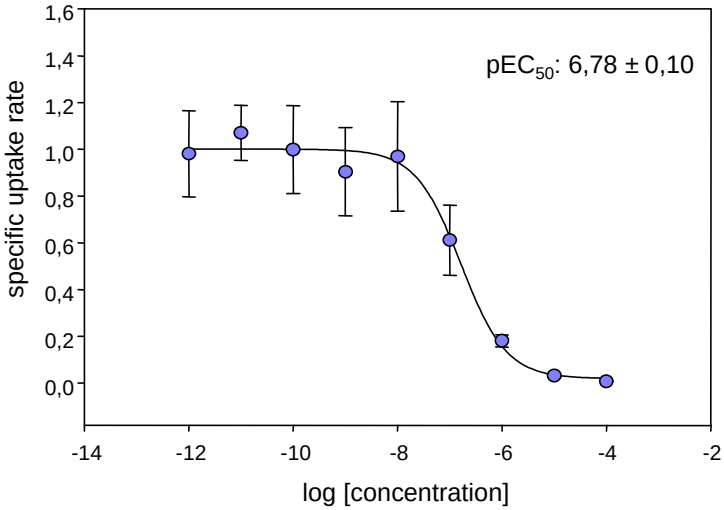
Stimulation of noradrenaline release from rat brain slices
by Thomapyrin®
Comparison with COMT- and MAO inhibition



Inhibition of serotonin uptake in JAR cells
by fluvoxamine



Effect of a substance under development
on neuronal GABA uptake



Enzymes as drug targets

Enzymes are excellent targets for pharmacological intervention, owing to their essential roles in life processes and pathophysiology. Not surprisingly, enzyme inhibitors represent almost half the drugs in clinical use today.

Diseases treated with enzyme inhibitors are as diverse as

- cancer,
- depression,
- pain,
- cardiovascular diseases,
- and erectile dysfunction.

Enzyme inhibition is a strategy, that can correct enzyme substrate deficiencies or an excess of enzyme product formation.

In recent years, the enzymatic modification of biological macromolecules (e.g. phosphorylation or acetylation of proteins) has come into the focus of drug research. Currently, we establish assays for these enzymes.

Enzyme inhibition experiments

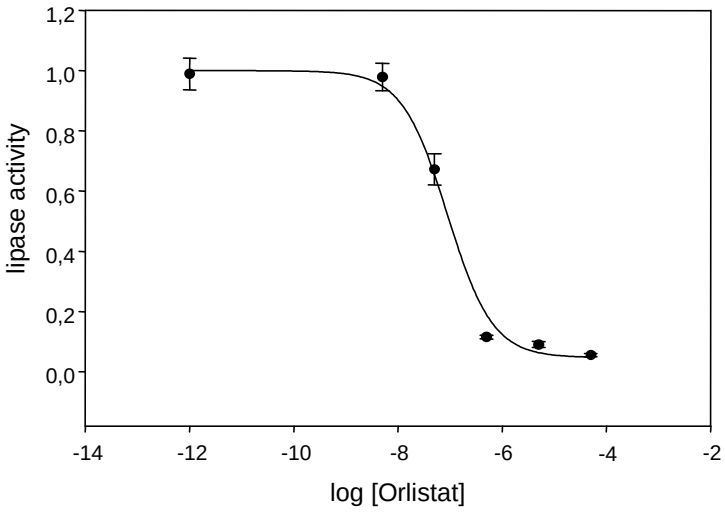
We offer assays for several enzymes involved in neurotransmitter synthesis and breakdown, including

- acetylcholinesterase
- butyrylcholinesterase
- GABA transaminase
- monoamine oxidases and others.

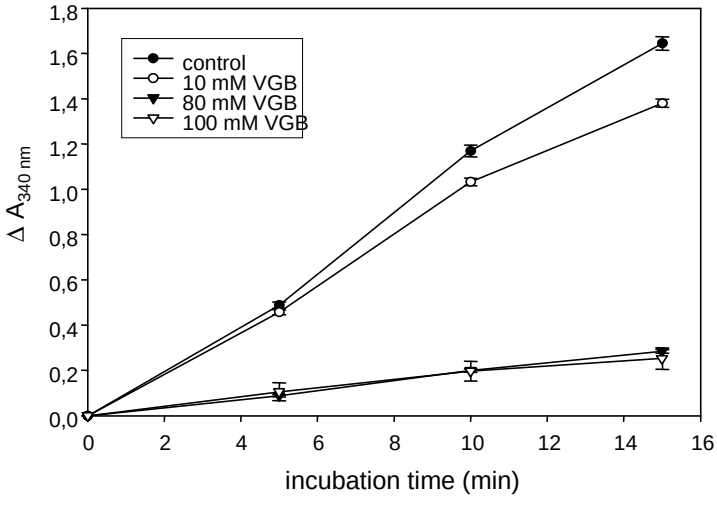
Assays can of course also be performed with non-CNS enzymes.

We are glad to provide you a specially designed enzyme assay for your pharmacological problem

Inhibition of porcine pancreatic lipase by orlistat



Inhibition of Pseudomonas fluorescens GABAse by vigabatrin



Your pharmacological questions - Our answers

You assume that your drug or drug candidate of interest acts on a specific molecular target.

Contact us and IBAM will suggest you suitable series of experiments, i.e.
• test conditions,
• test tissues (ex vivo, cell culture, etc.),
• measuring parameters,
and will conduct these experiments.

On completion of the study you obtain a scientific report of the results.

Do not hesitate to contact us. Our expert team will find the solution for your pharmacological problem.

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