5. Kooperationsforum
Drug Development
Strategien - Technologien - Therapien
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In vitro models for the determination of drug mode of action:

The melanin binding of drugs and its implications

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Melanin-containing tissues have been located in various parts of the human body: • skin • hair • eye • inner ear • brain substantia nigra (neuromelanin)	**Melanins have a multitude of physiological functions dependent on the tissue:** • protection from UV light • redox polymer • radical scavenger • sequestering of harmful substances (organic compounds, heavy metals)
Examples of drugs accumulating in melanin: • antimalarials (chloroquine) • neuroleptics (haloperidol, risperidone) • β-adrenergics (propranolol, metoprolol, timolol, clenbuterol) • antibiotics (amikacin, tobramycin) • carcinogenes (benzopyrene) • metal ions (iron, copper, lead, nickel)	**A contribution of melanin binding is established in several disorders:** • pigment disturbances of skin and hair, melanoma • ocular toxicity • ototoxicity • M. Parkinson, EPS • carcinogenicity of drugs Melanin binding also may influence drug delivery in pigmented tissues.

Affinity chromatographic determination of drug-melanin interaction

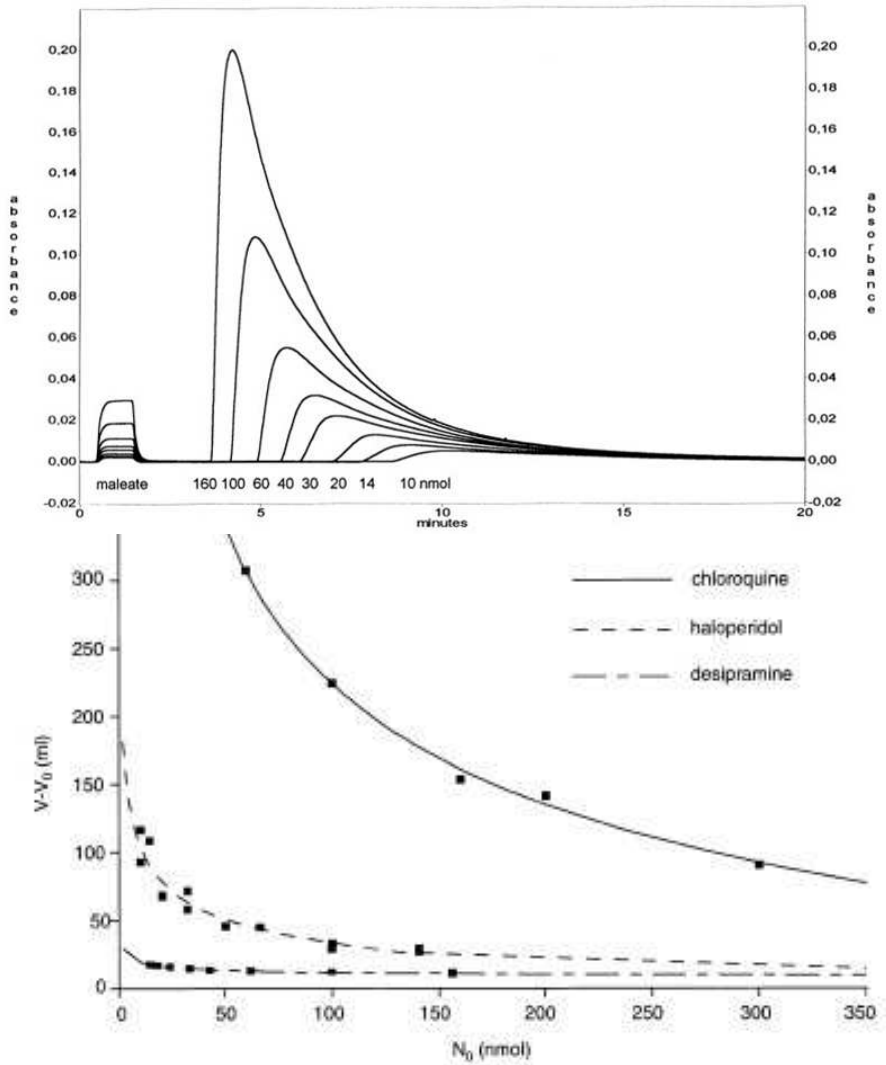

Fig. 3. Binding isotherms of chloroquine, haloperidol, and desipramine on synthetic L-DOPA melanin.

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.

Binding isotherms can be analysed using well-known algorithms (Scatchard, Freundlich, etc.) to obtain binding constants and number of binding sites.

Investigation of drug-drug interactions at the melanin binding sites

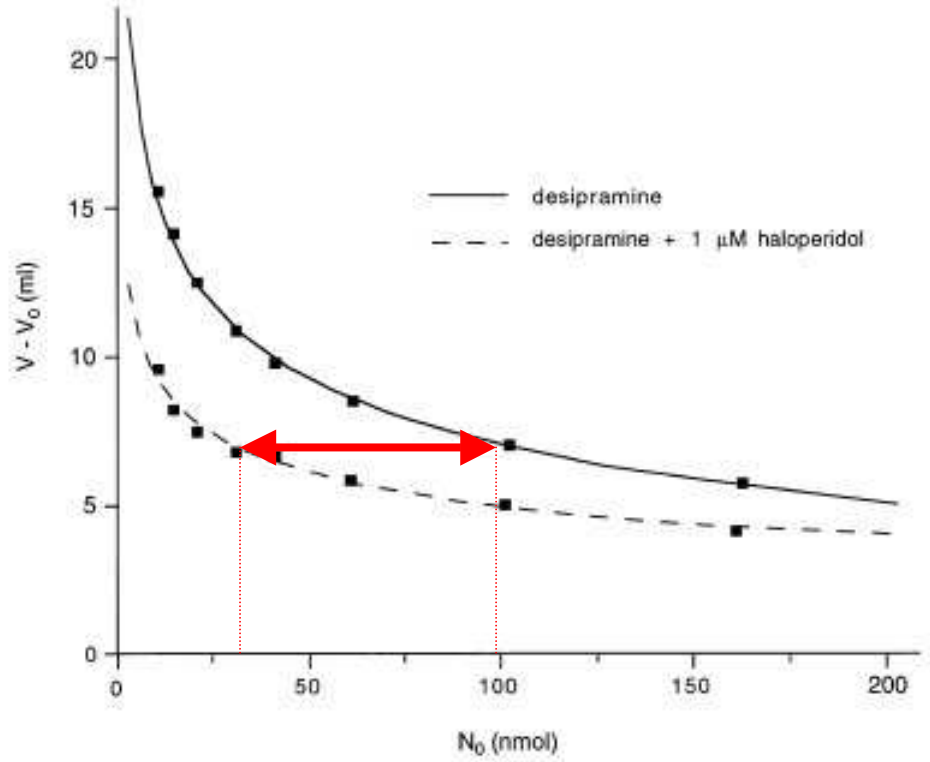

Fig. 4. Binding isotherms of desipramine on synthetic L-DOPA melanin in absence and presence of 1 μM haloperidol in the elution buffer.

The study of drug-drug interactions with melanin 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.

Physiological effects and adverse reactions caused by binding of pharmacologically active substances to melanin should be considered already in the phase of drug development!