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EDITORIAL

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Actions of psychotropic drugs beyond their primary targets at the synaptic cleft

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Psychotropic drugs not only bind to their primary target sites at the synapse, such as dopamine D_2 receptors or serotonin and noradrenalin transporters, but also to P-glycoproteins and metabolic enzymes. They also become protonated and bind to phospholipid structures, thereby frequently leading indirectly to inhibition of acid sphingomyelinase. These alternative binding sites sometimes lead to unexpected effects and should, therefore, be carefully considered in clinical situations. This special issue contains five publications, each dealing with mechanisms of psychotropic drugs beyond the primary target binding sites.

Interaction with P-glycoprotein: P-glycoprotein (P-gp), a 170 kDa ATP-dependent drug transport protein located in endothelial cells, plays an important role in protecting the brain from potentially harmful substances. P-gp is highly expressed in both intestinal epithelial cells and endothelial cells of brain capillaries and thus influences intestinal uptake and brain uptake of drugs. Interindividual differences in the expression and function of P-gp is a main determinant of uptake of endogenous toxins, psychotropic drugs and xenobiotics. For example, the accumulation of β-amyloid depends on the expression of P-gp in blood vessels [17], and the induction of Parkinson's disease by damaging effects of xenobiotics is influenced by the C3435T polymorphism of the ABCB1 gene [2]. This special issue contains two reviews on the role of the P-gp in the blood–brain barrier. The review by Ebinger and Uhr [3] focuses on the methods used to study P-gp, the substrates of P-gp and on genetic polymorphisms and effects on drug-response. The review by Thürauf and Fromm [15] also addresses the role of the P-gp transporter and provides selected examples for the role of P-glycoprotein for disposition and effects of centrally acting drugs and for the pathogenesis of CNS diseases such as Alzheimer's disease, Parkinson's disease and epilepsy. Both reviews highlight the importance of P-gp for understanding drug–drug interactions. Genetic factors determine P-gp expression and function and partly explain interindividual discrepancies in plasma-levels of certain drugs and central actions and side effects.

Interaction with CYP2D6 drug metabolizing enzyme: The interindividual variance in tolerability and therapeutic effects to psychotropic drugs are well known. In recent years, the importance of drug metabolizing enzymes and their polymorphic character has gained wide interest together with therapeutic drug monitoring. Poor CYP2D6 metabolizers can be reliably predicted by genotyping. Recently, a chip-based analysis of metabolizing enzyme has been introduced into clinical practice. In the near future, information about the polymorphic status of all relevant cytochrome P450 enzymes will be available for an individual patient. The situation is more complex in that there is a region-specific distrubution of cytochrome P450 enzymes in the human brain [14]. The paper by Thürauf and Lunkenheimer [16] summarizes the current knowledge on the metabolism of antidepressant drugs by cytochrome P450 enzymes.

Interaction with protons and phospholipids: Psychotropic drugs usually are amphiphillic and lipophilic. With these properties, the drugs sequestrate in brain tissue, reach high brain-to-blood concentration ranges and slowly disappear from the human brain [8]. In the article by Kornhuber et al. [12], a closer look is taken at the neuroleptic drugs haloperidol and levomepromazine. Long elimination half-lives in human brain tissue have been found with postmortem brain measurements [9–11], PET-studies [4] and MRS spectroscopy [1] with a variety of psychotropic drugs. With the high blood-to-brain concentration ratios and

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long elimination half-lives, the brain tissue acts like a sponge with a drug-depot, thus partly explaining long lasting effects and side effects of neuroleptic drugs. Direct measurement of drug-concentrations in human brain tissue obviously gives useful clinical information in addition to therapeutic drug monitoring in plasma or urine.

During the last decade, the monoamine theory of depression has proven to be too limited to explain the variety of changes in the brain and body of depressive patients. New pathways have been implicated in the pathophysiology of depression, such as altered neuroplasticity, inflammation and lipid metabolism. Different "new" neurotransmitters apart from monoamines were discovered. Interestingly, many of the older antidepressants as well as lithium or electroconvulsive therapy are also showing effects in these systems, a fact that might explain why some substances are more efficacious than others. The MAOI tranylcypromine is a potent antidepressant, but its use is limited to special indications such as therapy resistant depression. It exerts its effects on a broad variety of systems, which might contribute to its high efficacy. The review of Frieling and Bleich [5] in this issue focuses especially on its effects on phospholipid metabolism, trace amines, GABA receptors and cytochromes, implicating diverse effects of the drug on inflammation, neuroplasticity and neurodegeneration. Revisiting "old" but efficient drugs may help to generate more advanced models to understand the neurobiology of depression.

There are multiple crosslinks between the P-glycoproteins, metabolizing enzymes and storage of drugs in the brain due to acidotropic mechanisms:

- Compared to the neocortex, hippocampus and cerebellum, Cyp2D6 activity is low in the basal ganglia of the human brain [14]. One possible consequence is that drugs like phenothiazines with preferential metabolism by Cyp2D6 exhibit a region-specific distribution with higher concentrations in basal ganglia of the human brain compared to drugs with a less extensive metabolism by Cyp2D6 [12].
- The herbal medicine St. John's wort induces the drug metabolizing enzyme CYP3A4 and P-gp, resulting in severe drug interactions with the CYP3A4 and P-gp substrates cyclosporin and HIV protease inhibitors [6, 13].

Taken together, acidotropy and lipophilicity of psychotropic drugs as well as interactions with transport and metabolizing enzymes let us better understand interindividual differences in drug response, drug–drug interactions as well as hitherto unexplained clinical effects, like prolonged side effects after withdrawal of many of these drugs. There are further relevant interactions of psychotropic drugs beyond their primary targets at the synaptic cleft that are not covered by the articles in this special issue. One further example of alternative mechanisms of psychotropic drugs is the interaction with acid sphingomyelinase: This lysosomal enzyme catalyses the hydrolysis of sphingomyelin to phosphorylcholine and ceramide. Ceramide has multiple actions on cell membranes, signal transduction cascades, neurotransmitter receptors and transporters. Increased activity of acid sphingomyelinase has been found in major depression [7] and many antidepressant drugs notably inhibit acid sphingomyelinase [7].

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