Regional dopamine metabolism in the rat brain
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Dopamine (DA) plays an important role in neurotransmission processes in the brain. An interaction with dopaminergic mechanisms has been reported for several psychopharmacological agents, e.g. neuroleptics, psychostimulants like amphetamine and analgesics. It was the aim of the experiments, described in this thesis, to contribute to insight in the way centrally acting drugs interact with DA metabolism in the different dopaminergic systems in the brain.

In Chapter I various data consistent with the assumption that DA acts as a neurotransmitter were briefly summarized and some aspects of the metabolism and turnover of DA have been discussed. Chapter I further summarized the significance of some clinical chemical findings in relation to central DA metabolism.

In Chapter II a semiautomated fluorimetric assay for homovanillic acid (HVA) is described. The method is based on a rapid manually performed isolation of HVA on small columns of Sephadex G10 and an automated fluorimetric detection method. The method permits the determination of HVA in the striatum, nucleus accumbens and tuberculum olfactorium of a single rat brain.

The influence of such various HVA-increasing drugs as neuroleptics, morphine and cholinomimetics was studied in the striatal and mesolimbic dopaminergic systems (Chapter III). The results suggested that not only under normal conditions but also after treatment with various types of drugs and combination of drugs, dopamine metabolism as reflected by the HVA levels, is closely related in the different rat brain structures.

To achieve a more complete picture of DA metabolism, we developed a sensitive simultaneous assay of 3,4-dihydroxyphenylacetic acid (DOPAC) and HVA based on the isolation of the metabolites on Sephadex G10 columns (Chapter IV). These assays were applied to a study of the influence of amphetamine, apomorphine, morphine, oxotremorine, probenecid and various neuroleptics on DOPAC and HVA levels in the striatum, nucleus accumbens and tuberculum olfactorium. Clozapine, morphine, sulpiride and oxotremorine induced the most pronounced rise of DA metabolites in the nucleus accumbens. Probenecid produced a DOPAC accumula-
tation in the nucleus accumbens. Striking differences were observed between the DOPAC/HVA ratios in the different structures in control animals.

In Chapter V the disappearance of DOPAC and HVA from the brain of rats treated with a monoamine-oxidase inhibitor or a monoamine-oxidase inhibitor in combination with a catechol-O-methyl-transferase inhibitor was studied. The turnover of the metabolites was calculated by multiplying the steady state level by the fractional rate constant. The DOPAC turnover was found to be 23.3 nmol/g/h in the striatum and 22.6 nmol/g/h in the mesolimbic structures. The HVA turnover was 11.2 nmol/g/h in the striatum and 6.7 nmol/g/h in the mesolimbic structures. The data showed that under control conditions DOPAC is only partially O-methylated to HVA, while formation of HVA via the 3-methoxytyramine pathway is unlikely. DOPAC turnover therefore probably approximates DA turnover.

In Chapter VI we investigated the localization of DOPAC and HVA in various cortical areas. Confirming recent biochemical and histochemical findings our study showed the presence of DA metabolism in certain cortical regions of the rat brain. Various drug treatments suggested that DA metabolism in the frontal cortex shows similarities to that in mesolimbic tissue.

In Chapter VII the influence of various drugs on DOPAC and HVA levels in the substantia nigra and striatum of the rat brain was studied. Promethazine treatment caused a small but significant HVA rise in the substantia nigra only. Chloralhydrate, morphine and oxotremorine induced a similar percentage change in the metabolite levels in the substantia nigra as well as in the striatum. The time-effect curves for the substantia nigra showed an initial rapid HVA rise, which was not observed in the corpus striatum. Haloperidol, however, caused a small percentage change in the metabolite levels in the substantia nigra when compared to the pronounced rise seen in the striatum. The apomorphine-induced HVA decrease observed in both structures provides evidence for the presence of a DA receptor in the substantia nigra.

HVA levels were measured in the eye and the striatum (Chapter VIII) of untreated rats and after different drug treatments. Neuroleptics increased HVA levels in both structures, whereas apomorphine decreased HVA levels in the retina and the striatum. Morphine and oxotremorine induced a rise of HVA levels in the striatum but not in the retina. We concluded that comparison of the effect of various drugs on DA metabolism in the retina and the striatum can differentiate between drugs whose action is dependent on or independent of the connections of dopaminergic neurons with other neuronal systems.
In Chapter IX we have extended our observations on regional DA metabolism by studying the influence of 5 neuroleptics, 4 anti-depressants, 4 anti-epileptics, 4 anesthetics, propranolol and the anti-emetic agent metoclopramide on DOPAC and HVA levels in the striatum, nucleus accumbens and tuberculum olfactorium of the rat brain. To index drugs according to their relative potency for increasing DA metabolites in striatal versus mesolimbic brain structures, we calculated ratios of percentage DOPAC and HVA increase between the striatum and the two mesolimbic structures. Our earlier studies on this subject were included in this calculation. We were able to confirm that neuroleptics with a low frequency of extrapyramidal side-effects (clozapine, thioridazine and sulpiride) are differentiated from the classical neuroleptics by their ability to produce a relatively large increase in DOPAC and HVA levels in the two mesolimbic regions. However, the 14 non-neuroleptic drugs investigated all produced a relatively large increase of the dopamine metabolites in the two mesolimbic regions. We therefore concluded that, although there is clearly a distinction between the pattern of regional DA metabolism influenced by clozapine, sulpiride and thioridazine on the one hand and by the classical neuroleptics on the other, such an action is not specific and is therefore not necessarily related to the antipsychotic actions of these neuroleptics.

Chapter X deals with the effects of various midbrain lesions on the regulation of DA metabolism. We conclude that the described pallido-nigral feedback loop is not involved in the regulation of DA turnover following treatment of rats with amphetamine, apomorphine, haloperidol, morphine or oxotremorine. The dramatic and very acute increase of striatal DOPAC and HVA levels which we observed after partial lesioning of the dopaminergic axons, illustrates that dopaminergic neurons do not act in an uncoordinated fashion, and that very rapidly acting compensatory mechanisms are able to modify the output of this system. In addition we concluded, that the nerve impulse flow of dopaminergic cells seems to be a prerequisite for the effect of haloperidol, morphine and oxotremorine on striatal DA metabolism, whereas amphetamine and apomorphine are able to influence striatal DA metabolism independently of the nerve impulse flow.

In Chapter XI we described a minor modification of the DOPAC and HVA assay by which the amines noradrenaline, DA and 3-methoxytyramine could be sufficiently purified on Sephadex G10 columns to allow automated fluorimetric detection. The method permitted the concurrent measurement of noradrenaline, DA, 3-methoxytyramine, DOPAC and HVA in mg amounts of nervous tissue after one rapid and simple isolation step, with detection limits far below manual fluorimetric
alternative to be further used columns of alumina or ion exchange resin. We concluded that the small Sephadex G10 column is an excellent procedure.