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Investigations about the anxiolytic activity of the cholecystokinin-B-receptor-antagonist L365.260 in two animal-models of anxiety in rats

The identification of the neurobiological mechanisms of anxiety is a precondition for the development of pharmacological therapy strategies. The role of the involved neuronal transmission systems is of particular interest. The neuropeptide cholecystokinin (CCK) is supposed to play a role in the transmission of neuronal impulses in processes of anxiety. At least it could modulate other transmitting systems in sense of a positive or negative regulation. The CCK_B-receptor seems to play a major role in this process. Theoretically, inhibitors of CCK binding at the CCK_B-receptor are capable to suppress transmitter-related anxiety reactions. The aim of experimental research with CCK_B-receptor-antagonists is the development of clinically potent anxiolytics.

The benzodiazepin derivate L365.260 is a selective antagonist at the CCK_B-receptor. In two animal-models - a modified open-field as conflict-test and the elevated-plus-maze - the anxiolytic potential of L365.260 was evaluated for different dosages and administrations (centrally: into the ventricle and the hippocampus; peripherally: intraperitoneal) and under different surrounding conditions of different aversive potential (light, noise). Because Wistar-rats show different strain-dependent anxiety-related behaviours, Winkelmann-Wistar-rats (low trait-anxiety) and BgVV-Wistar-rats (high trait-anxiety) have been compared. All experiments were carried out using control-groups of vehicle-treated animals. The results were compared with the efficacy of so-called standard anxiolytics in the chosen experimental settings. Additional data were obtained for the efficacy of anxiety-inducing CCK_B-receptor-agonists and for one agonist of the serotonergic transmission system. Control trials have been performed to differentiate central effects from peripheral effects transmitted by the nervus vagus. A new simple inspectoric control procedure for the successful performance of the vagotomy has been established and validated. The plasmatic availability and the CNS-penetration have been proofed by plasma- and tissue-concentration measures.

After systemic administration, L365.260 shows a receptor-transmitted and dose-dependent effect, which can be neutralised by agonists. After central administration only minor effects can be shown. This might be due to the fact, that the inner anxiety status of the animals is changed by the central modus of administration. Looking at the inconsistent results obtained with the vagotomy trials one has to consider the traumatic stress of the operation to have a non calculable influence on the function of transmitter systems. Consistently a differentiation between the effects transmitted by central receptors and peripheral receptors or vagus receptors are not possible.

These results confirm the role of the CCK_B-receptor in the regulation of anxiety related processes. The inconsistent effects of the tested substances are similar to the results found in the literature and do underline on the one hand the distinct sensibility of animal-models for the evaluation of anxiety related processes to varying test conditions. On the other hand they show that the effects of single test substances can be different in different animal-models. The adoption of data obtained in animal-models to the pharmacobiological processes in human anxiety is therefore clearly limited.

The future investigation of potential anxiolytics like L365.260 should be intensified by using animal-models, with a more ethological approach in the interpretation and recording of behaviour displayed in the tests. For the acute central administration, experimental conditions should be developed, which do not influence the inner anxiety status of the animals. An increased receptor affinity of CCK_B-receptor-antagonists and a better CNS-permeability might be helpful improvements. Effects like tolerance and dependency, which haven't been described yet, have definitely to be excluded for clinical use. Therefore the effects of chronic treatment have to be further investigated to fasten the development of clinically usable anxiolytics.