6. SUMMARY

Development of a method for investigation impulsivity on rats : effect of selegiline and clomipramine

Impulsiveness is seen as a clinical symptom in several psychiatric disorders. It is used as a diagnostic criterion for impulsive-control disorders, personality disorders, borderline personality disorders, antisocial personality disorders and in mania. It can be found in the expression of different behaviours. In human medicine impulsivity is commonly linked to disorders such as impulsive aggression, violent behaviour, but also in drinking or sexual behaviour. In veterinary medicine impulsivity is not just referred to aggressive behaviour, what can be defined as reduction or a complete lack of warning signals previous to attack. It is probably also linked to behavioural disorders such as seperation anxiety, storm and noise phobia. Impulsivity is more a sign than a diagnosis itself.

So far, the construction of impulsiveness has not been sufficiently clarified. It has been proposed that there is an inverse relationship between the central serotonergic system and impulsive behaviour. Particularly the serotonergic metabolite 5-hydroxyindoleacetic (5-HIAA) seems to play an important role in the regulatory mechanisms of impulsivity.

Research in humans and animals demonstrates the association between impulsive behaviour resp. lack of impulsive-control with a decreased level of 5-HIAA.

It is a very important question how to measure impulsive behaviour. Some animal models have been developed, but not very extinsively. The delay of reinforcement method is one of the methods, which stand the test. Animals have to choose between a single pellet (small reinforcer) delivered immediately or a larger amount of food pellets (large reinforcer) delivered after a delay. The preference for the immediate reward, that means the intolerance to delay has been proposed to reflect impulsive behaviour, conversely, preference for the delayed reward would indicate self-contol.

The aim of this study is the development of a method for measuring impulsivity in rats, what does not exist in research institutes in Germany so far. Based on the delay of reinforcement method by EVENDEN and RYAN (1996) the present study used the Skinner Box with two different levers. The development of the method includes a period of four weeks for conditioning rats to combine lever pressing with emission of food. They also have to

distinguish between the two different levers. Rats were given the choice between a single food pellet (small reinforcer) delivered immediately or a large amount of 12 pellets (large reinforcer) delivered after a delay. Before using a conditioning program it is very important to figure out how many days for conditioning rats on lever pressing are required. Other components for developing a method for measuring impulsivity are also important, such as duration of the daily session, amount of food pellets as large reward and the maximum of delay before delivering the large reward.
With knownledge of all these aspects a conditioning program for rats has been developed. The conditioning of rats is the basic for using the delay of reinforcement. Three rat strains (Fischer/Winkelmann, Wistar/Winkelmann, Wistar/BgVV) were used. During the training session the Fischer/Winkelmann-rats did not explore the chamber and therefore did not start pressing the levers. The Fischer-rats were not suitable for the experiments of our study.

The pharmacological investigations were carried out on two different Wistar stocks (Wistar/Winkelmann and Wistar/BgVV). We investigated whether impulsive behaviour of Wistar/Winkelmann-rats and Wistar/BgVV-rats is affected by treatment with clomipramine, selegiline or diazepam.
The behaviour of Wistar/Winkelmann-rats was not significantly affected by treatment with clomipramine, whereas the number of lever presses by Wistar/BgVV-rats was decreased. Clomipramine reduced the activity of Wistar/BgVV-rats. Indeed, clomipramine had neither influence on impulsive behaviour of Wistar/Winkelmann-rats nor on impulsive behaviour of Wistar/BgVV-rats.
Selegiline significantly increased the activity of Wistar/Winkelmann-rats and Wistar/BgVV-rats, but did not influence the impulsive behaviour of both Wistar stocks.
The application of the highest dose of diazepam in our experiments induced an increase of the frequency of choice of the small reward by Wistar/Winkelmann-rats. Therefore, diazepam increased the impulsivity of Wistar/Winkelmann-rats. The impulsive behaviour of Wistar/BgVV-rats was not affected by treatment with diazepam.

In our study Fischer-rats and Wistar-rats showed different baseline levels of exploratory behaviour. Fischer-rats appear to be more „anxious“ than Wistar-rats.
Additionally, it appears that the different effects of diazepam on behaviour of Wistar/Winkelmann-rats and Wistar/BgVV-rats can be traced back to differences of their base impulsivity-related behaviour. Differences in the baseline behaviour might have an influence

on the effects of pharmacotherapeutics and could produce both false or negative results. Strain and stock differences should be taken into consideration in future investigations.

In conclusion, there is a necessity to develop new therapeutics agents for treatment impulsivity both in human medicine and veterinary science. Hence, further work is required on a similar approach to improve animal models for measuring impulsivity and beyond it getting specific knowledge of serotonergic processes in impulsive-related behaviour.