EFFECT OF AVANDAMET ON THE BEHAVIOR OF DIFFERENT AGE RATS

Gorbachenko V.A, Lukyanetz E.A.

Dept. Biophysics of Ion Channels, Bogomoletz Institute of Physiology, Kyiv, Ukraine

Abstract

The prevalence of Alzheimer's disease (AD) is increasing in the absence of truly effective treatments. The recently discovered causal link between AD and type 2 diabetes mellitus (T2DM) (non-insulin-dependent diabetes mellitus) suggests that an increase in insulin receptor resistance may affect brain aging and lead to AD. In our experiments, we tested Avandamet (AVD), the antidiabetic drug used for the treatment of T2DM, on temporary parameters of conditioning food reflex in rats. We measured the individual components of the sensorimotor reaction (SMR) of rats, which reflect CNS's functional state. Important that rosiglitazone is the main component of AVD. It acts by activating the nuclear peroxisome proliferator-activated receptor (PPAR) gamma. Our data showed that this drug influences the brain function of both young and old rats. It is proved that AVD affects the CNS of rats by increasing their excitability. Considering the obtained data from the point of view of AD, the time parameter, which changed more significantly in old rats, was responsible for analyzing the situation and speed of action. Under AVD's influence, old rats became more agile and had increased motor activity, also the success of rats in performing a conditioned reflex was increased. Thus, the drug AVD and its active component rosiglitazone can be perspective for its testing in AD treatment.

Methods

All experimental procedures were following the European Commission Directive. Experiments were carried out on female Wistar rats aged 3 and 15 months (n=20). We used control groups and treated with AVD for each age. AVD was administered at a dose of 4 mg/kg per os for 1 hour before the experiment. Old rats were used as a model of AD [4]. The automated device and software developed by ourselves [5, 6] were used to register the individual components of sensorimotor reaction (SMR) conditioned food reflex. The behavior registrations based on infrared sensors' operation registered the moving rats' paw in the feeding chamber's hole. In the rats placed in the main box, the skill, in response to a short sound, was developed to make search movements with a limb in a food feeder, reinforced after 2 seconds by feeding. The experiment's time course and several SMR time indicators were registered (described in the results). They allowed estimating CNS state, including memory working.

Results

During testing the food-getting reflex, we found that success was better in young rats. In the control group, the success of the conditioned reflex's manifestations in young rats was higher (91.6%) than in older ones (84.27%). In the older group, we observed greater variation of this indicator due to age-related difficulties in the extraction of information about conditioning stimuli. The conditioned reflex's success in old rats was increased (to 96,7%) under AVD to values of young group indicators. This parameter achieved 97.28% in young rats after AVD treatment. Thus, AVD substantially improved the success of the conditioned reflex in both age groups. The high success rate of the reflex (over 90%) may be the result of several factors: on the one hand - a reasonably strong link between the representations of the sensory and motor zones in the CNS. On the other - high food motivation. But, as already mentioned, since all animals were in the same conditions of food deprivation, the excitatory process's growth was caused by the action of the AVD.

We determined that while AVD did not affect the number of attempts required to pull food out of the food window (*RN*), the number of approaches to the trough window was significantly increased under this drug in both groups. This value was increased by 68,63% in young and 49,56% in old animals. It should be noted that the value was significantly higher in young rats than in old ones in control conditions. These experiments have shown that AVD enhances the CNS excitatory process, as evidenced by the increase in interstimulus reactions in both young and old rats.

Testing the SMR showed that in control experiments in young animals, search movements (*rt*) in an empty feeder after the conditional sound signal were twice as long as in old ones. The latter can be explained by the higher degree of CNS excitability characteristic of early life, rather than the high degree of food motivation, as rats of both age groups were previously on 24-hour food-deprived. AVD did not affect *rt* temporal characteristics in two groups of animals (Fig.1). After treatment with AVD, the time between individual food extraction movements (*TRr*) and the total time spent on extracting food balls from the feeder (*RT*) was decreased. Thus, in young rats, the value of *TRr* decreased by an average of 34.24% and 15.95% (p<0,05), respectively. The *RT* was found to be higher in young rats than in old in control. This can be explained by the fact of the low level of CNS excitation in old rats compared with young promotes a more accurate motor response both in control and under AVD. The time *RT* decreased in young rats under AVD's influence was 14.7% and 14.4%, respectively.

We determined that while AVD did not affect the number of attempts required to pull food out of the food window (RN), this drug significantly increased the number of approaches to the trough window (RNIS) in both rats' groups. Thus, AVD increased the value *RNIS* - the number of animal approaches to the food window position between the sound signals during the interstimulus period. *RNIS* was increased by 68,63% in young and 49,56% in old animals. In old rats, AVD also caused a decrease in *RD* value (the mean time of the limb staying in the food cell during the single attempt of obtaining the food) by an average of 15.95%, whereas, in young animals, this was changed not significantly (Fig.2).

The latent period of the sensorimotor response (*tl*) to the conditioned stimulus in control was more prolong in old animals than in young groups. But the speed of processing audio information by young animals was increased in the AVD group by 10.2%. In old rats, *tl* was not changed under the influence of AVD. Thereby, our data indicate that the antidiabetic drug AVD, which is used to treat T2DM, affects the CNS in young and old rats by increasing their excitability. AVD improved the manifestation of conditioned reflex in old rats (AD model).

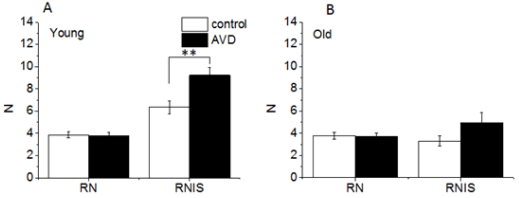

Fig.1. The average SMR values were recorded in control and under treatment with AVD in young (A) and old rats (B) are presented. The values are *RN*- the number of required attempts for getting food and *RNIS* – the number of approaches to the food window position between the sound signals during the interstimulus period. ** P< 0,01.

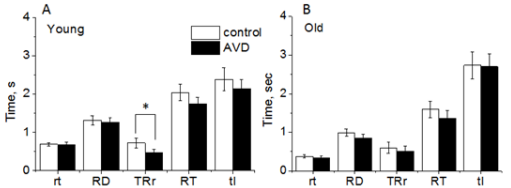

Fig.2. The average SMR values were recorded in control and after treatment with AVD in young (A) and old (B) rats. The values are *rt* - limb staying in the food window before supplying the food, *RD* - the mean time of the limb staying in the food cell during the single attempt of obtaining the food, *TRr* - the mean time between the attempts of obtaining the food, *RT* - total time of getting food from the feeder, *tl* - latent period, the time before the first the attempt of getting food after the sound stimulus. * P< 0,05.

Conclusions

AVD at a dose of 4 mg/kg increases the CNS's excitability, manifested by the several following facts:

increasing the number of interstimulus motor reactions;

Reducing the time of removing food balls from the feeder, i.e., increasing the speed of individual phases of food movements. This trend is manifested regardless of the high state of motor excitability in young animals in control;

Increase in individuals in a group of older animals the probability of reflex manifestations (the ability to extract from the "memory cells" the significance of the sound signal, which triggers the sequence of food movements).