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16

Two Types of Epilepsy Models and Processes of Cognition: Pentylenetetrazole Kindling and Absence Epilepsy of WAG/Rij Rats Strain

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1. Introduction

In many studies a fundamental difference between two types of generalized epileptic activity, convulsive epilepsy and absence non-convulsive epilepsy was described. All forms of convulsive epilepsy, both in human and animal models, are characterized by increased activity of excitatory amino acid transmitter systems (Hara et al., 2006; Leke et al., 2006; Schilling et al., 2006) and/or decreased activity of the inhibitory GABAergic system (Bazyan et al., 2001b; Quilichini et al., 2006; Laschet et al., 2007) of the brain. The main difference between absence non convulsive epilepsy and convulsive epilepsy is in a fact that pharmacological stimulation or inhibition of excitatory glutamate synaptic transmission causes relative enhancement or reduction of the severity of absence epilepsy (Ngomba et al., 2005; Citraro et al., 2006), and increased GABAergic inhibition also leads to enhanced absence epilepsy (Coenen et al., 1995; Bouwman et al., 2003; 2004).
The next fundamental difference between absence epilepsy and other generalized epilepsy forms consists in the profile of epileptic discharge. Usually, convulsive epileptic discharges appear on the wave of excitation. The gradual growth of excitation reaches the threshold level after which epileptic discharges appear. During absence epilepsy, the discharge is fundamentally different. A spike–wave discharge consists of an inhibitory phase and an action potential. The inhibitory phase is represented by a slow wave on an EEG. The spike is an indicator of cell excitation (action potential). A rebound spike appears at the end of the inhibitory period, and the cycle repeats again and again (Midzianovskaya et al., 2001).
In this paper we compared mechanisms underlying two kinds of epileptic activity, pentylenetetrazole kindling and absence epilepsy, and their interaction with processes of learning, memory, emotional and motivational states.

2. Pharmacological reminders restore benzodiazepine site density of $GABA_A$ receptors and conditioned memory: Allosteric plasticity and intraneuronal integration by the help of transduction signal

Interaction of BDZ with its own site activates slow endocellular metabolic reactions through activation of protein kinase C (Niles et al., 1997; Nomura et al., 1997; Johnston et al., 1998),

induces transductional signal and modifies genes expression. In this connection $GABA_A$ receptor subunit protein expression is reduced (Johnston et al., 1998), while the c-fos gene expression is induced (Niles et al., 1997). Neuroactive steroids are analogs of steroid hormones, but unlike them they interact with somatodendritic and postsynaptic $GABA_A$ receptors (Rupprecht, Holsdoer 1999). Interaction of neuroactive steroids with $GABA_A$ receptor triggers a process of oxygenation, which transforms some endocellular metabolites into ligands of endocellular steroid receptors. After linkage of ligands with receptors an expression of genes occurs.

Thus, BDZ site of the $GABA_A$ receptor induces intracellular slow metabolic reactions via a protein kinase C-dependent mechanism (Niles et al., 1997; Nomura et al., 1997; Johnston et al., 1998; Ghori et al., 2010; Bignante et al., 2010). In the first part of our study (Bazyan et al., 2001b) we investigated long-term components, apparently metabolic components of $GABA_A$ supramolecular complex in convulsive states, specifically, long-term characteristics of [^{3}H]–diazepam binding in the cerebellar cortex after an acute injection of PTZ in convulsive doses.

Acute PTZ treatment

Male Wistar rats were used. The first series comprised the rats endogenously sensitive and resistant to the PTZ. In PTZ-sensitive animals, seizures provoked a significant decrease in the B_{max} of [^{3}H]–diazepam binding by 16% versus control and by 14% versus resistant rats at 30 minutes after the termination of seizures, with no change in the K_d. No differences in [^{3}H]–diazepam binding between the control and resistant rats at 1 hour after the PTZ treatment and the control, sensitive and resistant rats on day 7 after the PTZ treatment were found. These results show that initially the characteristics of [^{3}H]–diazepam binding to BDZ site in the sensitive and resistant rats were similar, but the PTZ treatment induced a greater response of BDZ receptors in sensitive rats versus resistant rats. It means that sensitive animals show more intensive allosteric regulation of BDZ site of $GABA_A$ receptor by PTZ than resistant rats. On day 7 the characteristics of [^{3}H]-diazepam binding came back to the initial level. This type of reaction reflected the efficiency of BDZ site allosteric regulation by PTZ as opposed to "initial activity", when the characteristics of diazepam binding are different initially.

The second series comprised the rats, in which a convulsive dose of PTZ (50 mg/kg) resulted in seizure scores of 4 to 5 points. They were sacrificed 1 hour or 48 hours later and on day 7 after the PTZ treatment. The density (B_{max}) of [^{3}H]–diazepam binding sites was significantly reduced by 19% at 1 hour after the PTZ treatment and by 16% at 48 hours with no change in the K_d. No significant changes were found on day 7.

PTZ-induced kindling. Acquired sensitivity

The third series comprised the rats, in which a subconvulsive dose of PTZ (20 mg/kg, once daily for 24 days) elicited kindled seizures scoring 4 to 5 points. They were sacrificed 1 hour or 48 hours later and on day 7 after the last injection. The rats with kindled seizures scoring 4 to 5 points were selected from the total population of animals. Daily injections of PTZ (20 mg/kg) resulted in a gradual increase in sensitivity to PTZ (Bazyan et al., 2001b) and a significant decrease in the B_{max} of [^{3}H]–diazepam binding by 19% at 1 hour after the PTZ treatment and by 16% at 48 hours after the last injection. The binding K_d was unchanged. On day 7, no significant changes were observed (Fig. 1A). These findings in the kindled rats are similar to the results found after an acute administration of the convulsive dose. Thus, kindling led to the establishment of a new level of the BDZ site allosteric regulation by PTZ, because PTZ interacts with PCT site and modifies binding of [^{3}H]–diazepam with BDZ site.

The high efficiency of the BDZ receptor allosteric regulation, which is produced by administering PTZ daily at subconvulsive doses, is termed "allosteric plasticity". This procedure induces a long-term, high sensitivity to low PTZ doses, which is determined by the decreasing of BDZ site density in the cerebellar cortex that occurs 48 hours after the termination of PTZ treatment with no change in the K_d, and subsequent normalization on day 7 (Fig. 1A), therefore, the allosteric plasticity formed the basis for the development of high sensitivity to PTZ.

It is known that kindling can lead to a long-term decrease of the $GABA_A$ receptor complex density, due to changes in the synthesis of the respective proteins. A series of 40 kindling-induced seizures (by rapid hippocampal stimulation) led to biphasic alterations of $GABA_A$ receptor subunit mRNA levels in dentate gyrus with only minor changes in CA_1-CA_3 (Kokaia et al., 1994). Up to 4 hours after the last seizure the expression of mRNA for α1 subunit was slightly decreased in dentate gyrus, whereas marked reductions were observed for β3 and γ2 subunits. Between 12 and 48 hours there were major increases of α1 (by 59%) and γ2 (by 35%) subunits mRNA levels but no significant changes of β3 subunit mRNA expression. The subunits mRNA levels returned to control values in 5 days. These results are similar to ours (Fig. 1A). The biphasic changes of $GABA_A$ receptor subunits may be related to their recombination.

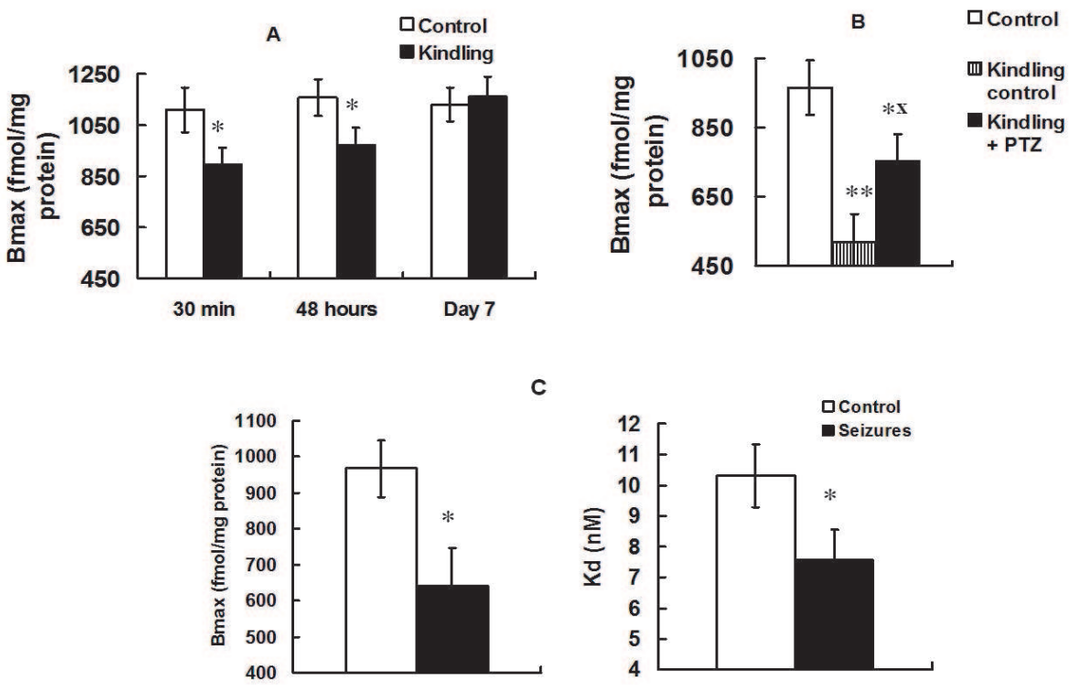

Fig. 1. Effects of chronic PTZ treatment and subsequent PTZ challenge on [^{3}H]–diazepam binding to membranes from the cerebellar cortex of 3- to 4-months and 10-months rats. **A**, BDZ site density (B_{max}) in 3- to 4-months-old rats kindled with PTZ at a dose of 20 mg/kg. *p_t < 0.05 versus control (n = 6 in each group). **B**, BDZ site density (B_{max}) in 10-months-old kindled rats challenged with PTZ (+ PTZ) at a dose of 30 mg/kg. **p_t < 0.01, kindled versus control; *p_t < 0.05, kindled + PTZ versus control; $^x p_t$ < 0.05, kindled + PTZ versus kindled control (n = 6 in each group). **C**, BDZ site density (B_{max}) and affinity (K_d) in 10-months-old rats after acute seizures induced by PTZ at a dose of 30 mg/kg. *p_t < 0.05 versus control (n = 6 in each group).

After 6 months (about 10-months-old rats)

For the period of 6 months both the control and kindled rats were kept in the breeding facility. At the second stage, the persistence of kindling was studied. Two control groups and two groups of kindled rats were treated with 20 and 30 mg/kg PTZ (Bazyan et al., 2001b). The kindling response of high sensitivity to low PTZ doses was preserved through the 6-months rest period after the kindling treatment, but not completely and with some attenuation. A subconvulsive dose of PTZ (20 mg/kg) induced no seizures in the control rats but elicited seizures in 60% of the kindled rats (1 to 2 points). At the next dose of PTZ (30 mg/kg) seizures were observed in 56% of the control rats (maximal scores of 2 to 3 points) and in 100% of the kindled rats (maximal scores of 3 to 4 points).

For the study of [^{3}H]-diazepam binding four groups of animals were used (Bazyan et al., 2001b): 1) control rats, no PTZ challenge; 2) acute seizures control rats, 30 min after the termination of acute seizures (2 to 3 points) induced by a PTZ (30 mg/kg) challenge; 3) kindled control rats, no PTZ challenge, but with a history of seizures (4 to 5 points) 6 months ago; 4) kindling + PTZ challenge, 1 hour (30 min after the termination of seizures, 3 to 4 points) induced by a PTZ (30 mg/kg) challenge.

In the kindled control rats with a history of seizures (4 to 5 points) 6 months before, the B_{max} of [^{3}H]–diazepam binding was reduced to 54% with no change in K_d without a PTZ challenge (Fig. 1B). It was shown above that the development of kindling represented the development of allosteric plasticity. But 6 months later the BDZ site activity was found to be modified. We may suggest, therefore, that allosteric plasticity is an intracellular process and the decrease in BDZ site density 6 months after the kindling reflected an ongoing intracellular process.

After a PTZ challenge, the B_{max} of [^{3}H]-diazepam binding in the kindled rats was found to be enhanced to 78%, still being significantly lower than in the control rats, with no change in the K_d. This paradoxical finding can be logically explained as follows. At the time of termination of kindling (Fig. 1A), the BDZ site density is reduced to 80.97% versus the control 4-months-old rats. After a rest period of 6 months, there was a decrease in BDZ sity density to 53.57% in the kindled rats without a PTZ challenge. Acute PTZ administration to the kindled rats induced seizures and partially restored the BDZ site density, just to the level of BDZ density found in the control 10-months-old rats (77.77%, Fig. 1B), which was established 6 months before. At the same time, the K_d of BDZ site binding was unchanged in the kindled rats, whereas in the control 10-months-old rats that had seizures after a single PTZ challenge BDZ receptors density B_{max} and K_d was significantly altered. The PTZ (30 mg/kg) challenge in the ten-months-old intact rats resulted in seizures (acute seizures, scores 2 to 3 points) which were accompanied by a decrease in both indices of [^{3}H]–diazepam binding: the B_{max} to 66%, and the K_d to 73% (Fig. 1C). We suggest that the PTZ challenge acted as a reminder to the kindled animals, reproducing the modification of BDZ site acquired 6 months ago, irrespective of their current status and animal's age.

The increased density of BDZ site of $GABA_A$ receptors (versus the kindled control) can be interpreted as an enhancement of GABAergic inhibition, while it is thought that seizures are based on the process of neuronal hyperactivation accompanied by a reduction in the BDZ site density both in kindling-induced (Fig. 1A) and single-dose PTZ-induced seizures. Therefore, it is likely that at 6 months, when seizures are retrieved by a PTZ challenge and the level of GABAergic inhibition is restored, the level of glutamate receptors may also be restored, assuming that they were modified and consolidated in the process of kindling 6

months ago. The level of glutamate receptors may only be restored of neuronal GABA and glutamate receptors interact within a single integrated system interconnected through intracellular transduction signal.

The interaction and integration of neuronal GABA and glutamate receptors has been shown in several studies. Thus, in PTZ-induced kindling the reduction in GABAergic functions is blocked by MK-801, an antagonist of NMDA receptors (Corda et al., 1992). NMDA receptors are involved in the process of kindling induced by FG 7142, an inverse agonist of the BDZ receptor (Stephens & Turski, 1993). Also, the NMDA-induced long-term potentiation is found to be controlled by the intercellular metabolic systems of the $GABA_A$ receptor complex, being inhibited by BDZ site agonists (Evans & Viola-McCabe, 1996; Higashima et al., 1998) and facilitated by its antagonists (Stackman et al., 1996; Seabrook et al., 1997). Positive allosteric activation of $GABA_A$ receptors bi-directionally modulates hippocampal glutamate plasticity and behaviour (Shen et al., 2009). BDZ withdrawal anxiety is associated with potentiation of AMPA receptor currents in hippocampal CA1 pyramidal neurons attributable to increased synaptic incorporation of GluA1-containing AMPA receptors (Shen et al., 2010).

The differences in BDZ reaction between the PTZ-sensitive and PTZ-resistant rats (Bazyan 2001b) can be accounted for by differences in the intensity of allosteric regulation of the $GABA_A$ receptors, based on differences in their subunit composition. We propose, accordingly, that the acquisition of high level allosteric regulation by the kindled rats is best explained by the intracellular metabolic feedback mechanism which is schematically shown in Fig. 2. In this scheme, PTZ interacts with the PCT site of $GABA_A$ receptor and modifies the BDZ site and $GABA_A$ receptor, which in turn alter the concentration of second messengers. The second messengers can modify phosphorylation reactions by changing protein kinase activities. The cycle is closed by modifications of GABA and BDZ sites, leading to changes in density as well as some redistribution of their subunits. In the process of kindling the cycle is repeated again and again, resulting in further decreases of the $GABA_A$ receptor complex. Protein kinases can modify gene expression, acting via a secondary nuclear signal and altering the synthesis of the subunits forming the $GABA_A$ receptor complex, whereby the reduced density, redistribution of the receptor subunits and, ultimately, the acquired efficiency of allosteric regulation or allosteric plasticity are consolidated.

As indicated above, changes in cellular phosphorylation levels by protein kinases can modify glutamatergic receptors augmenting their responses to endogenous excitatory amino acids. The metabolic regulation of a glutamatergic synapse (Fig. 2) is similar to that described for hippocampal neurons (Mayford et al., 1995). We added a feedback loop for metabolic regulation controlled by NMDA receptors in the hippocampus or by mGlu1 receptors in the cerebellum, since we assume that the feedback metabolic regulation, or autoregulation of glutamatergic and GABAergic receptors, is a necessary condition for maintaining the processes of long-term potentiation and long-term depression. The regulation of AMPA receptors and autoregulation of NMDA receptors in the hippocampus have been studied experimentally (Bayazitov & Kleshchevnikov, 2000).

Thus, one can assume that plasticity is a result of cooperative activity of GABA and glutamatergic receptors integrated into interrelated system. Integration includes also automodification of receptors activity. Further, a new level of activity, produced by secondary intranuclear signals modifies genes expression and consolidates a newly developed activity of receptors.

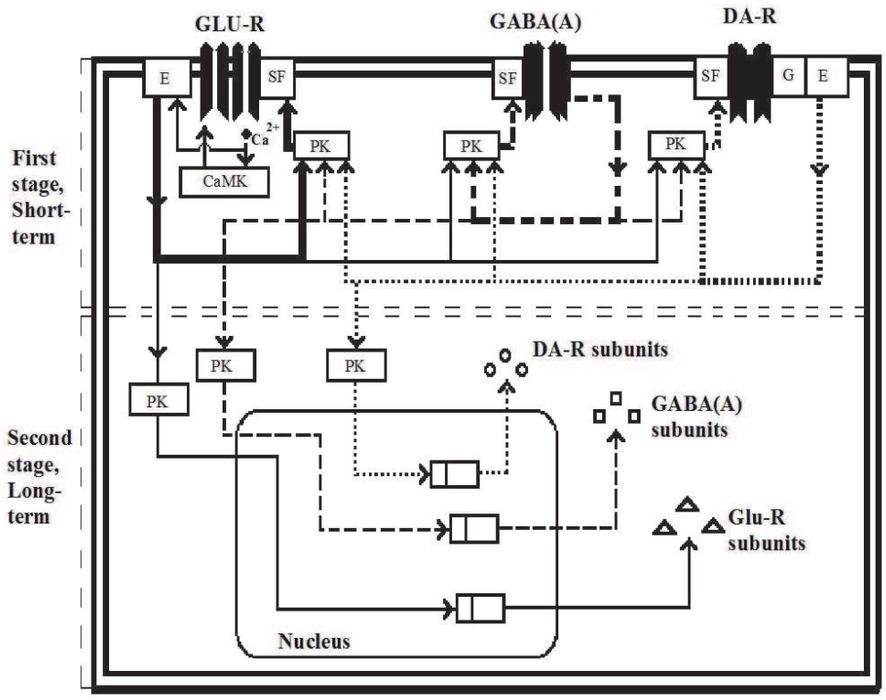

Fig. 2. A tentative model of intraneuronal metabolic integration. GLU-R, glutamatergic receptors; GABA(A), $GABA_A$ receptor; DA-R, dopamine receptor; E, second messenger synthesizing enzyme; SF, phosphorylation substrate; G, G-protein, PK, different type of protein kinases; CaMK, calcium/calmodulin-dependent protein kinase. Metabolic reactions mediated by glutamatergic receptors are shown as *solid lines*. Metabolic reactions mediated by $GABA_A$ receptor are shown as *dashed lines*. Metabolic reactions mediated by dopamine receptors are shown as *dotted lines*. Intracellular metabolic feedback loops (autoregulation) are shown as the respective *thick lines*. For other details, see in text.

Interaction of PTZ-induced seizures with learning, memory and emotional state

It is well known that a convulsive state is an amnesic state. It is also known that convulsive disorders are accompanied by mental disorders, such as anxiety and fear, or depressive states (Clement et al., 1997; Depaulis et al., 1997; Maxudova & Flesher, 1998). At the same time, anxiogenic effects of PTZ are also known [Biggio et al., 1990; Venault et al., 1992; Simon et al., 1993]. It was shown [Bazyan et al., 2000b] that haloperidol–induced catalepsy, which produces a long-term modification of DA receptors, is modified by defensive conditioning. So, the next investigation [Bazyan et al., 2001a] was designed to study the modification of seizures by learning; the facilitation of amnesic memory trace retrieval by a pharmacological reminder of the emotional state which accompanied the learning processes. Passive avoidance conditioning was performed (Bazyan et al., 2001a). The rats were divided into three groups according to their levels of learning: *group I* - high level of learning; *group II* - middle level of learning; *group III* - low level of learning. PTZ was injected 75 mg/kg and 50 mg/kg i.p. immediately after the learning session of group I and group II accordingly. Amnesia provoked by PTZ seizures was found on days 2. Unconditioned reminder acted as an unamnesic agent for group I and evoked memory retrieval on day 2. The effects of pharmacological reminder were studied in groups II and III on day 2 (Bazyan et al., 2001a).

After conditioning retrieval testing some rats in group II were treated with PTZ (30 mg/kg i.p.). The rats in which PTZ elicited seizures were excluded from further experiments. Haloperidol, a nonselective dopamine (DA) D_2 antagonist, was administered (0.25 mg/kg i.p.) to some rats in groups II and III. The amnestic effect of the convulsive PTZ dose of 50 mg/kg was canceled by a lower, subconvulsive doze of 30 mg/kg, as well as by haloperidol at a low doze of 0.25 mg/kg. The low doze of haloperidol 0.25 mg/kg facilitated memory retrieval in the animals of group III. At the same time, this doze of haloperidol had no effect on the latency of moving into the dark compartment in untrained animals. The effects of a low dose of haloperidol were studied in a separate series of experiments. Rats were treated with haloperidol (0.25 mg/kg, i.p.). Haloperidol at 0.25 mg/kg provoked "freezing". Catalepsy was not shown. Herewith, the rats showed the typical pose of fear (hunched), the number of dejections was also increased (Bazyan et al., 2001a). Thus, the amnesic memory trace is expected to be reproduced by chemicaly different anxiogens, such as haloperidol. Hence the mechanism of reflex retrieval is related to the mechanism of emotional state retrieval.

The mesocorticolimbic DA system is a reward and reinforcement system, directly involved in learning and memory (Wise, 1978, 2009; Joseph et al., 2003; Bazyan, & Grigoryan, 2006). The nigrostriatal DA system basically controls activity of GABA and glutamatergic receptors of middle spiny neurons of dorsal striatum, which regulates a motor function (Greengard, et al., 1999; Mink, 2003). Also, the DA system is involved in the modification of various epileptiform states (Al Tajir & Starr, 1991; Ogren & Pakh, 1993; Amabeoku & Chikuni, 1994). The results shown in our work (Bazyan et al., 2000b), allow us to suggest that in the process of learning the receptors of the DA system and $GABA_A$ receptors of the brain interact and become modified and integrated, thus forming a learning-depended emotional state. We suggest that this integration is accomplished by the mechanism of intracellular integration of glutamate, $GABA_A$ and DA receptors by means of transduction signal. The intracellular integration by transduction signal of glutamate, $GABA_A$ and DA receptors is schematically shown in Fig. 2. DA receptors can undergo automodification by the metabotropic feedback loop and then modify the activity of glutamate and $GABA_A$ receptors by intracellular phosphorylation [Greengard et al., 1999]. Via the same reactions of intracellular phosphorylation, glutamate and $GABA_A$ receptors can control the efficiency of DA receptors. At the second stage, the modifications established at the first stage are consolidated through the modification of expression of the respective genes. The ability of DA receptors to undergo automodifications has been demonstrated both at the level of radioligand binding and at the level of gene expression in various brain structures and various experimental procedures (Soghomonian, 1993; Qin & Weiss, 1994; Richtand et al., 2010).

Thus, PTZ induced seizures cause amnesia and dissociation state. Low subconvulsive PTZ doses restore a memory trace. Low PTZ doses have also anxiogenic effect. As active avoidance is based on anxiogenic state it may be restored by induction of the anxiogenic state by PTZ. Haloperidol, another anxiogenic compound in low subcataleptic doses is able to restore an amnesic memory trace. It seems that DA receptors are also involved in endocellular integration together with GABA and glutamatergic receptors and all rules of endocellular integration described for GABA and glutamatergic receptors are also applied for DA receptors.

3. Absence epilepsy of WAG/Rij rat's strain

Absence epilepsy in men and in WAG/Rij (Wistar Albino Glaxo, from Rijswijk) rats is a genetic animal model of generalized human absence epilepsy (Midzianovskaya et al., 2001;

Van Luitelaar & Coenen, 1997; Meeren et al., 2002), which principally differs from convulsive forms of epilepsy. For example, a number of widely used anticonvulsants enhance absence epilepsy (Coenen et al., 1995; Hosford & Wang, 1997; Bouwman et al., 2003; 2004; Maris et al., 2006; Tolmacheva & van Luijtelaar, 2007). A series of spontaneous spike-wave discharges (SWD) induced by hyperpolarization appear on a normal EEG. The SWDs in EEG of WAG/Rij rats start at about 2-3 months. At the age of six months, all rats have several hundred SWDs per day. The generalized and widespread bilaterally presented synchronous SWDs are the result of highly synchronized oscillations in the thalamocortical network. SWDs have a local cortical origin in the perioral region of the somatosensory cortex (Meeren et al., 2002; 2009; van Luijtelaar & Sitnikova, 2006). Besides, there is another strain of rats with absence epilepsy deduced GAERS (Genetic Absence Epilepsy Rats from Strasbourg) similar to WAG/Rij rats.

There are two other features, which make WAG/Rij rats as a valid model of human absence epilepsy: 1) The changed expression of genes coding low threshold Ca^{2+} channel of T – type ($\boldsymbol{I}_{\mathbf{Ca,T}}$) of WAG/Rij compared to ACI control rats (Broicher, et al., 2008) and mutation of genes coding $\boldsymbol{I}_{\mathbf{Ca,T}}$ by people with absence epilepsy (Vitko et al., 2007; Arias-Olguín, et al., 2008); 2) Local variations of $GABA_A$ receptors subunit expression in thalamo–cortical systems (Liu, et al., 2007) of WAG/Rij rats and mutation of genes coding subunits of $GABA_A$ receptors in people with absence epilepsy (Bowser, et al., 2002; Kang & Macdonald, 2004).

Chlorine conductance of the $GABA_A$ receptor at absence epilepsy and PTZ kindling

In the study [Rebrov et al., 2007], we determined the features of the functional activity of the $GABA_A$ receptor (intensity of chloride current) in WAG/Rij rats with a genetic predisposition to absence epilepsy and Wistar rats at an early stage of kindling development (absence epilepsy) and after kindling (generalized tonic–clonic seizures). Muscimol was found to dramatically increase $^{36}Cl^-$ conductivity in synaptoneurosomes of the brain cortex after its addition to the incubation medium as compared to the basal level in all groups of animals. We found a fundamental difference between the muscimol-induced $^{36}Cl^-$ conductivity of synaptoneurosomes from the brain cortex (frontal and somatosensory areas) of the convulsive PTZ-treated Wistar rats and WAG/Rij rats with absence epilepsy. Development of the tonic–clonic kindling induced a significant decrease in muscimol-induced $^{36}Cl^-$ conductivity in neocortical synaptoneurosomes as compared to the control rats. The muscimol-induced $^{36}Cl^-$ conductivity of synaptoneurosomes from the somatosensory and frontal cortex of the control WAG/Rij rats was considerably higher than in the control Wistar rats.

The high muscimol-induced $^{36}Cl^-$ conductivity in the neocortical synaptoneurosomes of the WAG/Rij rats corresponds to the hyperpolarization-induced nature of spike-wave discharges in absence epilepsy (Inoue et al., 1993; Midzianovskaya et al., 2001; Meeren et al., 2002; 2009; Maris et al., 2006) and the presence of a cortical focus in the somatosensory cortex (Meeren et al., 2002; 2009; van Luijtelaar & Sitnikova, 2006). This proposal agrees with the pharmacological results that describe regulation of spike-wave discharges by activation or inhibition of WAG/Rij rats GABA system (Peeters et al., 1989; 1990; Coenen et al., 1995; Hosford & Wang, 1997; Bouwman et al., 2003; 2004; Maris et al., 2006; Tolmacheva, van Luijtelaar, 2007). Our results, obtained in animals with nonconvulsive kindling, which is an experimental model of absence epilepsy (Caddick & Hosford, 1996; Snead 1996; 1998), also point to an increase in the activity of the $GABA_A$ receptor via intensification of the chlorine current.

Thus, two types of generalized seizures are accompanied by opposing changes in the $GABA_A$-mediated $^{36}Cl^-$ conductivity inside neocortical synaptoneurosomes. $^{36}Cl^-$ conductivity decreased in rats with PTZ-induced convulsive kindling and increased in rats with a genetic predisposition to nonconvulsive absence epilepsy.

Cognitive processes in WAG/Rij rats

Learning and memory

It is known that SWDs are controlled by the DA-ergic system of the brain. Antagonists of D2 DA receptors increase and agonists decrease of SWDs (De Bruin et al., 2000; Deransart et al., 2000; Midzianovskaya et al., 2001). It is possible the opioid system of brain also controls SWDs (Lason et al., 1990; 1992; 1994a; 1994b; 1995; Przewlocka et al., 1995). It is very well known that the mesocorticolimbic DA-ergic system is the system of reinforcement; it actualizes an emotional positive state and is also involved in processes of learning and memory (Wise, 1978, 2009; Joseph et al., 2003; Bazyan, & Grigoryan, 2006). The opioid system controls the threshold of pain sensitivity and actualizes the motivation of escape and avoidance of pain (Baranauskas, & Nistri, 1998; Bazyan, et al., 2000a;). An infringement of WAG/Rij rat's behavior was shown (Bazyan et al., 2000c; Sarkisova and Kulikov, 2000). The decrease of memory reproduction, spontaneous catalepsy, low threshold of haloperidol-induced catalepsy and the actualization of depression were found in WAG/Rij rats. All these data can be explained by a DA deficit of WAG/Rij rat brain. The goal of the investigation (Getsova et al., 2003; 2004) was to study the possibility of WAG/Rij rat's behavior correction by pharmacological activation of DA-ergic system.

The procedure of passive avoidance is described above. The defensive conditioned reflex of two-way avoidance was established in a shuttle-box. There were three series of experiments. First series: disulfiram (25 mg/kg i.p.), inhibitor of dopamine–β–hydroxylase, was administered to Wistar and WAG/Rij rats 4 hours before the 1st day learning session. Second series: L-DOPA (25 mg/kg i.p.) was administered to Wistar and WAG/Rij rats 4 hours before the 1st learning session. In the 3rd series of experiment disulfiram (25 mg/kg i.p.) was administered immediately after 1st learning session in Wistar and WAG/Rij rats. Saline was administered i.p. in the same number of control Wistar and WAG/Rij rats. An amnesic reaction in control WAG/Rij rats versus control Wistar rats was found in day 2 of the passive avoidance conditioning procedure. The administration of disulfiram before as well as after passive avoidance conditioning increased the reflex reproduction on the next day after learning both in Wistar and WAG/Rij rats. The reproduction of passive avoidance memory was increased 1,34 and 1,41 times in Wistar rats and 4,21 and 4,89 times in WAG/Rij rats accordingly.

The administration of disulfiram 4 hours before establishment of active avoidance conditioning changed the learning processes in the first day. It was shown that control WAG/Rij rats realized 2,23 times more avoidance reactions than control Wistar rats in the first day of learning. Disulfiram administration before learning decreased the number of avoidance responses in the first day: in Wistar rats 1,47 times and in WAG/Rij rats 6,45 times. In the second day of learning an amnestic effect in control WAG/Rij rats versus control Wistar rats was found. The index of memory trace storage of WAG/Rij rats was 2,11 times lower than in Wistar rats. The administration of disulfiram increased the memory trace storage of Wistar rats in 1,44 times and in WAG/Rij rats 7,33 times. The other inductor of DA system activation, L-DOPA, a precursor of DA synthesis, was used for comparison. Synergic effects of disulfiram and L-DOPA administered 4 hours before learning were

found. The administration of L-DOPA 4 hours before learning decreased the number of avoidances in the first day of learning in Wistar rats 1,76 times and in WAG/Rij rats 7,65 times. Herewith, the index of memory trace storage was increased in Wistar rats 1,82 times and in WAG/Rij rats 7,70 times. The high number of avoidances in WAG/Rij rats on the first day of active avoidance conditioning was found earlier (Bazyan et al., 2000c; 2001). We explain this reaction by the low efficiency of opioid system in WAG/Rij strain (Lason et al., 1990; 1992; 1994a; 1994b; 1995; Przewlocka et al., 1995) and as a consequence a low pain threshold and a high level of escape and avoidance motivation. It is shown (Altier & Stewart, 1998; 1999; Calabrese 2001) that activation of the DA-ergic system evokes analgesic reaction including activation of the opioid system (Suaudeau & Costentin, 1995; Cook et al., 2000; Magnusson & Fisher, 2000; Gao et al., 2001; Trekova et al., 2001). It was suggested that a deficit of dopaminergic system in WAG/Rij rats is the biological correlate of these behavioural deficits and that an enhanced sensitivity to DA-ergic agents is the consequence of this deficit.

DA activity in WAG/Rij rats

Further we studied some parameters of DA activity in WAG/Rij rats in attempt to find their deficiency. The goal of our first experiment (Midzianovskaya et al., 2004) was to investigate DA and its metabolites, DOPAC and HVA concentration in the following brain structures of Wistar and WAG/Rij rats: frontal cortex, parietal cortex, medulla, striatum, thalamus and cerebelum. Concentrations of DA and its metabolites have been defined by method of high performer's liquid chromatography. There was no difference in dopamine concentration in WAG/Rij versus to Wistar rats. But the changes of dopamine metabolites concentration and relation HVA/DA in some structures were substantially different for WAG/Rij and Wistar rats. There was a significant reduction of DOPAC concentration in striatum, and of HVA concentration in thalamus in SWDs rats. Reduction of metabolites concentration in the thalamus and striatum is related to enhancement of DA activity in these structures. The strengthening of DA activity may occur as compensation for DA deficiency at behavioural level. The deficiency of dopaminergic activity is likely to be linked with changes of DA receptors. In order to test such probability we compared (Birioukova et al., 2006) D_1 and D_2/D_3 DA receptors binding sites in some brain areas of WAG/Rij rats. DA receptors-binding sites were analysed using *in vitro* autoradiography.

A significant reduction of [^{3}H] SCH 23390 binding sites density with D_1 DA receptors of WAG/Rij rats compared to ACI rats in the shell of nucleus accumbens and in the head of caudate nucleus is seen. In other structures the significant changes are not observed. A significant increase of [^{3}H] spiperone binding sites density with D_2/D_3 DA receptors of WAG/Rij rats compared to ACI in motor, somatosensory and parietal cortex is seen. In the head of caudate nucleus and in the hippocampal CA3 area of WAG/Rij rats the [^{3}H] spiperone binding sites density with D_2/D_3 DA receptors is substantially lower than in the same structures of ACI rats. In the other structures there are no signifint differences on these measures. Our results show a deficiency of mesolimbic (NAcb shell) and mesocortical (motor, somatosensory and parietal cortex) DAergic activity at the level of somatodentritic D1– up-regulated and D2–like down-regulated DA receptors in WAG/Rij versus to ACI rats. At the same time a deficiency of nigrostriatal DAergic system in the head of caudate nucleus caused by reduction of D1-like DA receptors density is compensated by reduction of D2-like DA receptors density. The deficiency of mesocorticolimbic DA systems corresponds to behavioral features of WAG/Rij rats. During active and passive avoidance a

deficit of reinforcement in WAG/Rij rats has been revealed (Getsova et al., 2003; Getsova et al., 2004) which was eliminated by administration of the DA precursor, or a low doze of disulfiram, inhibitor of dopamine–β–hydroxylase, by increase of DA concentration in brain. Besides, there was shown that WAG/Rij rats have a higher level of depression than control Wistar rats without of absence epilepsy (Sarkisova et al., 2003; Sarkisova & Kulikov 2006). Depression of WAG/Rij rats has a DA-ergic nature (Sarkisova et al., 2008). The high depression of WAG/Rij rats may be explained by deficiency of the DA mesocorticolimbic system.

The question arises then. If the absence epilepsy is related with disturbance or mutation of $GABA_A$ receptor and low-threshold Ca^{2+} channel of T-type then what is a role of DA receptors in it. Why there is a functional deficiency of these receptors seen? We suggest that diminished activity of DA receptors and DA system deficit occur due to disruption of intracellular integration triggered by transductional signal (Fig. 2). The initial disruption of $GABA_A$ receptor activity disrupts transductional signal on the first stage induced by this receptor. Disruption of transductional signal changes modification of other receptors and their activity. On the second stage the disrupted activity of receptors is consolidated and stored by expression of genes. It should be noted that we did not practically see the changes of DA concentrations in structures investigated but could see the changes of receptors activity. So, a process of intracellular integration may disrupt activity of other neurotransmitter and neuromodulatory systems, for instance activity of opioide system disrupted in WAG/Rij rats (Lason et al., 1990; 1992: 1994a; 1994b; 1995; Przewlocka et al., 1995).

Our results (Birioukova et al., 2006; Rebrov et al., 2007) confirm the idea that absence epilepsy is connected with function of the hyperpolarization–induced cyclic nucleotide–gated pacemaker $\boldsymbol{I_h}$ channel, which subunits are expressed in thalamic neurons (Clapham, 1998). Recent studies have shown (Strauss, 2004) that subunits of $\boldsymbol{I_h}$ channel are expressed in neurons of the somatosensory cortex of WAG/Rij rats.

Hyperpolarization–activated *I*h pacemaker channel during absence epilepsy

Hyperpolarization–activated cyclic nucleotide–gated cationic $\boldsymbol{I_h}$ pacemaker channels maintain spontaneous periodic activation, which was discovered in the brain. In all, four isoforms of this channel are known (HCN1–HCN4, hyperpolarization–activated and cyclic nucleotide–gated) (Bazyan & Segal, 2010). The HCN channel is open at an average membrane potential of –80 mV. However, different subunits of the HCN channel possess different functional properties. For example, HCN1 channels become activated five to ten times faster than HCN2 channels. Also, HCN1 channels become activated at a membrane potential that is 20 mV more positive than the potential required for HCN2 activation. The HCN1 channel demonstrates minimal response to cAMP binding (+4 mV) to the cAMP–binding domain on the C–terminus (see Bazyan & Segal, 2010), whereas the HCN2 channel demonstrates a clear response (+17 mV). Coexpressed heteromultimeric channels demonstrate a relatively larger shift in response to cAMP (+14 mV).

The literature reviewed suggests that the $\boldsymbol{I_h}$ channel and low–threshold T–type Ca^{2+} channel ($\boldsymbol{I_{Ca2+,\,T}}$) work in tandem (Bazyan, Segal, 2010). Hyperpolarization opens the $\boldsymbol{I_h}$ channel, and cationic current depolarizes the membrane to the threshold and induces a spike. Hyperpolarization also opens the $\boldsymbol{I_{Ca2+,\,T}}$ channels. The entrance of Ca^{2+} ions into the cell induce Ca^{2+}–dependent cAMP synthesis, and cAMP dramatically increases channel activity through binding to the CNBD locus of HCN subunits. The HCN1 subunit responds weakly

to cAMP binding, therefore, a decrease in the proportion of HCN1 subunits in the channel increases pacemaker activity and an increase in the proportion of HCN1 subunits in the channel decreases pacemaker activity.

Several studies have focused on I_h channel activity during absence epilepsy. The fast component of I_h activation in neurons of WAG/Rij rats was significantly reduced (a 50% decrease in the current density), and was four time slower than in the neurons of nonepileptic Wistar or ACI rats (Strauss et al., 2004). The results of Western blot and PCR analysis corresponded to a decreased I_h current. A decrease by 34% was found in the level of the HCN1 subunit protein in the cerebral cortex of WAG/Rij rats as compared to Wistar rats but HCN1 mRNA had stable expression. The protein and mRNA levels of the other three I_h channel subunits (HCN2–HCN4) were not altered (Strauss et al., 2004). These results suggest that there are substantially fewer HCN1 subunits in the combined complex of the I_h channel in WAG/Rij rats than in rats of the control strains. This fact allows one to make the assumption that these channels work substantially more slowly but possess higher activity than the I_h channels of Wistar and ACI rats. High activity is defined, for example, by insignificant modification of the HCN1 subunit after cAMP binding, whereas modification of the HCN2 subunit is stronger. This means that the increase in the proportion of the HCN1 subunit in the channel complex decreases its response to cAMP binding, and, in contrast, the channel with more HCN2 subunits and less HCN1 subunits in its composition functions better.

It has been already shown that neonatal handling and mother deprivation in the early childhood of WAG/Rij rats (during postnatal 1-21days) result in reduced seizures and decreased interspike interval and frequency spectrum power of spike–wave discharges of adult WAG/Rij rats (Schridde & van Luijtelaar, 2005). Whole cell patch–clamp recordings from the cells of the fifth pyramidal layer, in situ hybridization, and Western blot analysis of the cortex of adult WAG/Rij rats (Schridde et al., 2006) showed an increase in the HCN1 protein level in the somatosensory cortex of handled and mother–deprived rats as compared to control rats. This increase was selective for the HCN1 subunit and did not affect the expression of HCN2–HCN4 subunit proteins, neither did expression of the mRNA of any subunit (HCN2, HCN3, HCN4). These results indicate that relatively mild changes in the environment of neonatal rats have long–lasting consequences for paroxysm activity and suggest that increased concentration of the HCN1 subunit in I_h channel composition is related to reduced absence epileptic activity. It was demonstrated that genetic absence epilepsy is highly susceptible to early interventions that lead to increased I_h current and higher concentrations of the HCN1 subunit as compared to control rats. However, the level of mRNA and protein of HCN2, HCN3 and HCN4 subunits did not differ in control and WAG/Rij rats (Schridde et al., 2006). These results indicate that the I_h channel plays an important role in the generation of seizures in a specific small area of the somatosensory cortex, and may be simply explained by alterations in the subunit composition of I_h channel, namely, an increased proportion of HCN1 subunits.

4. Conclusion

We have described that efficiency of allosteric regulation depends on subunits structure of $GABA_A$ receptor. We came to conclusion that the subunits composition of $GABA_A$ receptor in sensitive and resistant rats is different. The results assume that allosteric plasticity of

$GABA_A$ receptor and its consolidation are related with modification of subunits expression which finally lead to modification of $GABA_A$ receptor subunits structure. PTZ induced seizures cause amnesia and dissociation state. Low subconvulsive PTZ doses restore a memory trace. Low PTZ doses have also anxiogenic effect. Haloperidol, another anxiogenic compound in low subcataleptic doses is able to restore an amnesic memory trace. The process of plasticity represents a cooperation and integration of GABA, glutamate and DA receptors into interdependent systems. Its integration includes automodification of receptors activity. On the second stage, a new level of activity, by means of secondary intranuclear signals induce modification of genes expression, which consolidates a newly developed activity of receptors.

Two types of generalized seizures are accompanied by opposing changes in the muscimol-indused $GABA_A$-mediated $^{36}Cl^-$ conductivity. GABA reaction decreased in rats with PTZ-induced convulsive kindling and increased in WAG/Rij rats with a genetic predisposition to nonconvulsive absence epilepsy. In the shell of nucleus accumbens the lower density of D1-like DA receptors was found. The results specify deficiency of mesolimbic dopaminergic system activity of WAG/Rij rat brain that corresponds to specific behavioral characteristics of WAG/Rij rats and to pharmacological experimental data. It has been assumed that the source of spike–wave discharges was the $\boldsymbol{I_h}$ pacemaker channel that is localized in the thalamic reticular nucleus and in the pyramidal neurons of the somatosensory cortex layers three, four, and five. The analysis of the experimental data shows that one of the basic mechanisms for the long–term regulation of $\boldsymbol{I_h}$ pacemaker activity is the modification of the number of HCN1 subunits in the pacemaker channel of WAG/Rij rats strain.

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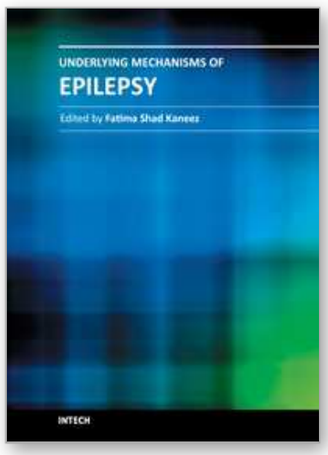

Underlying Mechanisms of Epilepsy

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This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

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