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Research report

The role of NMDA and AMPA/Kainate receptors in the consolidation of catalepsy sensitization

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ABSTRACT

Daily injection of the dopamine D_2 receptor antagonist haloperidol is associated with the development of catalepsy sensitization in rats, which leads to a day to day increase of rigor and akinesia. The process of catalepsy sensitization incorporates different learning stages. Here we investigated the mechanisms underlying the consolidation of catalepsy sensitization. In particular, we asked whether NMDA- and non-NMDA (AMPA- and Kainate) receptors play a role in the consolidation of catalepsy sensitization. Accordingly, rats received post-training injections of the NMDA receptor antagonist MK-801 (single injection of either 0.1 mg/kg or 0.25 mg/kg; or a double injection of 0.1 mg/kg immediately and 30 min after test cessation) or of the AMPA/Kainate receptor antagonist GYKI 52466 (single injection of 5 mg/kg). Our results showed that the consolidation of catalepsy sensitization was decelerated by both glutamatergic AMPA/Kainate- and NMDA-receptor antagonists. With the higher MK-801 dosage, the deceleration was stronger, suggesting a dose dependent mechanism. We hence affirmed a role for the ionotropic glutamate receptors in the consolidation process of catalepsy sensitization.

1. Introduction

Haloperidol induced catalepsy (HIC) is a well accepted animal model for the Parkinsonian symptoms akinesia and rigor and can be reliably quantified by movement initiation latency measurement [1,2]. Antagonism of dopamine (DA) D_2 receptors with haloperidol leads to hyperactivity of the indirect, striatofugal pathway within the dorsal basal ganglia loop [3,4], disinhibition of the major output structures of the basal ganglia, and finally to an increased inhibition of thalamo-cortical neurons. Under constant conditions, repeated daily catalepsy testing with a preceding haloperidol injection leads to a gradual decline in motility, corresponding to a gradual increase in HIC [5]. Previous work has shown that this gradual increase in HIC is based on a specific learning process that is commonly referred to as behavioural sensitization. While the classically understood sensitization refers to the gradual increase of a behavioural effect to the repeated administration of a DA agonist – usually a psychostimulant [6,7] – sensitization processes are also involved in the progressive aggravation of rigor and akinesia in Parkinson's disease: repeated administration of a DA antagonist results in a day to day decrease in activity, i.e. an increase in catalepsy [8]. Thus, sensitization to stimulants and HIC might follow similar rules but in opposite directions, facilitating appropriate and suppressing inappropriate motor commands [9–11].

A recent study classified HIC-sensitization as a form of the so called "no-go" learning [12], one of two learning processes that are important during the completion of planned actions. Frank et al. [13] developed a series of neurocomputational models in which they demonstrated that two main populations of medium spiny neurons in the striatum have opposing effects. Whereas an activity of the so called "go" neurons facilitate the execution of a motor action (synaptically modulated by the DA D_1 Pathway), the activity of the "no-go" (modulated via the DA D_2 Pathway) neurons prevent or suppress the execution of competing motor actions. The comprehension of the selection of "go" (in our model the leaving of an inconvenient position) versus "no-go" (in our model persisting in an inconvenient position) mediated movements is important not only for control of daily movements but also for the understanding of diseases with disturbed action selection (i.e. in Parkinson's disease and schizophrenia).

Furthermore HIC-sensitization is described as an associative learning process, which is strongly dependent on the context [14–16] and/or the animal's internal state (interoceptive cues) [5]. The robustness of this association process was already shown [14,15]. The described properties of HIC-sensitization lead to the presumption that this learning paradigm follows the same rules as other associative learning processes [17,18]. In general, learning phases can be subdivided into acquisition (development of

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an association), consolidation (conversion from labile to more stable memory storage and hence the induction of long-term-potentiation (LTP) or long-term-depression (LTD)) and expression (retrieval of learned associations). In this study, we explicitly focussed on the consolidation of HIC-sensitization and the role of ionotropic glutamate receptors during that learning stage, since these receptors are evidently involved in processes of neuronal plasticity which plays an essential role in acquisition, consolidation and reconsolidation [19–26]. In the present study, we administered the selective non-competitive NMDA-receptor-antagonist MK-801 or the non-competitive AMPA/Kainate receptor-antagonist GYKI 52466 [27–29] directly after cessation of the catalepsy test to unequivocally assess whether the respective receptors are necessary for the consolidation of HIC-sensitization.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (250–280 g bodyweight (BW), Charles River, Sulzfeld, Germany), were used in all experiments. Animals were housed in groups of four per cage under a 12/12 h light–dark cycle with restricted access to food (Ssniff special-diet – standard dried pellets 12 g per animal per day) and water *ad libitum*. For the first experiment we used 7 or 8 animals per group, for the second experiment 10 animals per group and for the third experiment 12 animals per group.

2.2. Substances

Haloperidol (Janssen-Cilag GmbH, Neuss, Germany) was diluted in saline with a concentration of 0.5 mg/ml in the first and second experiment and in aqua injectabilia (Ampuwa, Fresenius Kabi, Bad Homburg, Germany) in a concentration of 0.25 mg/ml in the third experiment.

The NMDA receptor-antagonist [(5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate] (dizocilpine hydrogen maleate (INN), MK-801, Sigma–Aldrich, Steinheim, Germany) was dissolved in saline. For the first experiment a concentration of 0.1 mg/ml (once or twice) was used and for the second experiment concentrations of 0.1 mg/ml and 0.25 mg/ml were used. All concentrations were related to free base. The above-named substances were administrated intraperitoneally in an injection volume of 1 ml/kg BW.

The AMPA/Kainate receptor antagonist GYKI 52466 (a generous gift from Dr. Tarnawa, Budapest, Hungary) which was used in the third experiment was diluted in aqua injectabilia to a concentration of 5.0 mg/ml and administered intraperitoneally as 1.0 mg per kg BW. The concentration of GYKI 52466 was related to free base.

2.3. Behavioural testing

Catalepsy was first assessed on a horizontal bar (18 cm length, 0.8 cm diameter, 8 cm above the test table surface) by placing the animal's forepaws onto the bar. Immediately afterwards animals were tested on a vertical wire-mesh grid (25 cm × 40 cm surface area; 1 cm mesh width) by placing the animal with all four paws onto the grid. For both tests, the time was measured until the animal actively displaced one paw (descent latency). Testing took place during the light phase on nine consecutive days. The respective glutamate receptor antagonist was administered directly after the catalepsy test. Animals were tested 60 min after haloperidol or vehicle injection. To avoid physical fatigue of the animals, every catalepsy test was cut off after 180 s. As mentioned above, the injection of one glutamate receptor antagonist was applied directly after the grid test. For the first and second experiment this second injection was the NMDA receptor antagonist MK-801 or its vehicle. In the first experiment, one group received an additional injection 30 min after that second injection. For the third experiment, the AMPA receptor antagonist GYKI 52466 or its vehicle was applied.

2.3.1. Experiment 1

In the first experiment, a total of 23 animals were used which were subdivided into three groups. The first group (positive control group, $n = 8$) received a vehicle injection directly after the catalepsy test. The second group (1× MK-801 group, $n = 8$) received one MK-801 injection (0.1 mg/kg BW) directly after the catalepsy test. The third group (2× MK-801 group, $n = 7$) received two MK-801 injections, one directly after the catalepsy test and the second injection 30 min later.

2.3.2. Experiment 2

For the second experiment, we used four groups ($n = 10$ in each group). The positive control group received a haloperidol injection before and a vehicle injection after the catalepsy test.

The two groups which were used to test the effect of MK-801 had a haloperidol treatment first. A second injection was applied after the catalepsy test consisting of a MK-801 injection of 0.1 mg/kg BW within one treatment group (MK-801 0.1 group) or 0.25 mg/kg BW in the other treatment group (MK-801 0.25 group). The negative control group received a vehicle injection at each time point instead of haloperidol and a post-test vehicle injection, respectively.

2.3.3. Experiment 3

For the third experiment, we used a total of 24 animals separated in two groups ($n = 12$ for each group). Like in the first and second experiment we had a positive control group that received only vehicle directly after the catalepsy test. The testing group (GYKI group) received the AMPA receptor antagonist GYKI 52466 5.0 mg/kg BW directly after the catalepsy test.

2.4. Statistical analysis

For all statistical tests we used the software GB STAT professional, version 7.0 (Dynamic Microsystems, Inc.). All data are presented as means ± standard errors (SEM). Data were analysed using a two-way analysis of variance (ANOVA, treatment × time) followed by post hoc Fisher's LSD test when appropriate.

3. Results

3.1. Experiment 1

All groups of the first experiment showed a significant development of HIC-sensitization in the bar test (Fig. 1A, two-way ANOVA: $F(8, 160)_{time} = 48{,}75$, $p < 0.0001$). However dependent on treatment, the development was different between groups ($F(16, 160)_{treatment \times time} = 1{,}99$, $p = 0.016$). For the grid test a significant effect over time was observed (Fig. 1B, two-way ANOVA: $F(8, 16)_{time} = 18{,}71$, $p < 0{,}0001$).

The descent latencies extracted from both testing apparatuses indicated an obvious delay of HIC-sensitization in the MK-801 treated groups compared to the positive control group with the stronger effect in the 2× MK-801 group.

3.2. Experiment 2

In the second experiment the comparison between the negative control group and the positive control group was carried out separately in order to test the validity of the positive control group. Two-way ANOVA revealed a significant difference between the negative and positive control groups in the bar test ($F(1, 18)_{treatment} = 27{,}98$, $p < 0.0001$, $F(8, 144)_{time} = 6{,}53$, $p < 0.0001$, $F(8, 144)_{treatment \times time} = 6{,}44$, $p < 0.0001$) as well as in the grid test ($F(1, 8)_{treatment} = 19{,}75$, $p = 0.0003$). The positive control group showed significantly higher decent latency from day three to day nine ($p < 0.01$) in the bar test and from day two to day nine ($p < 0.01$) in the grid test according to post hoc test Fisher's LSD (significances not shown in Fig. 2A and B).

The positive control group and both MK-801 0.1 group and MK-801 0.25 group developed significant HIC-sensitization over time in the bar (Fig. 2A) and the grid (Fig. 2B) test (two-way ANOVA: bar: $F(8, 216)_{time} = 15{,}83$, $p < 0.0001$; grid: $F(8, 216)_{time} = 3{,}87$, $p = 0.0003$). Additionally, treatment with MK-801 led to a trend in reduction of descent latency compared to the positive control group in the bar test (two-way ANOVA: $F(2, 27)_{treatment} = 3.15$, $p = 0.058$).

Thus the higher MK-801 dosage led to a stronger deceleration of HICs than the lower MK-801 dose. Furthermore there was generally a weaker effect in the grid test concerning the HICs over all haloperidol treated groups.

3.3. Experiment 3

The comparison of the positive control group and GYKI group showed significant differences for the treatment and development of HIC-sensitization over time (two-way ANOVA: $F(1, 22)_{treatment} = 6{,}91$, $p = 0.0153$, ($F(8, 176)_{time} = 13{,}48$, $p < 0.0001$) in the bar test (Fig. 3A)). In the grid test (Fig. 3B) a significant difference was observed over time ($F(8, 176)_{time} = 27{,}76$, $p < 0.0001$)

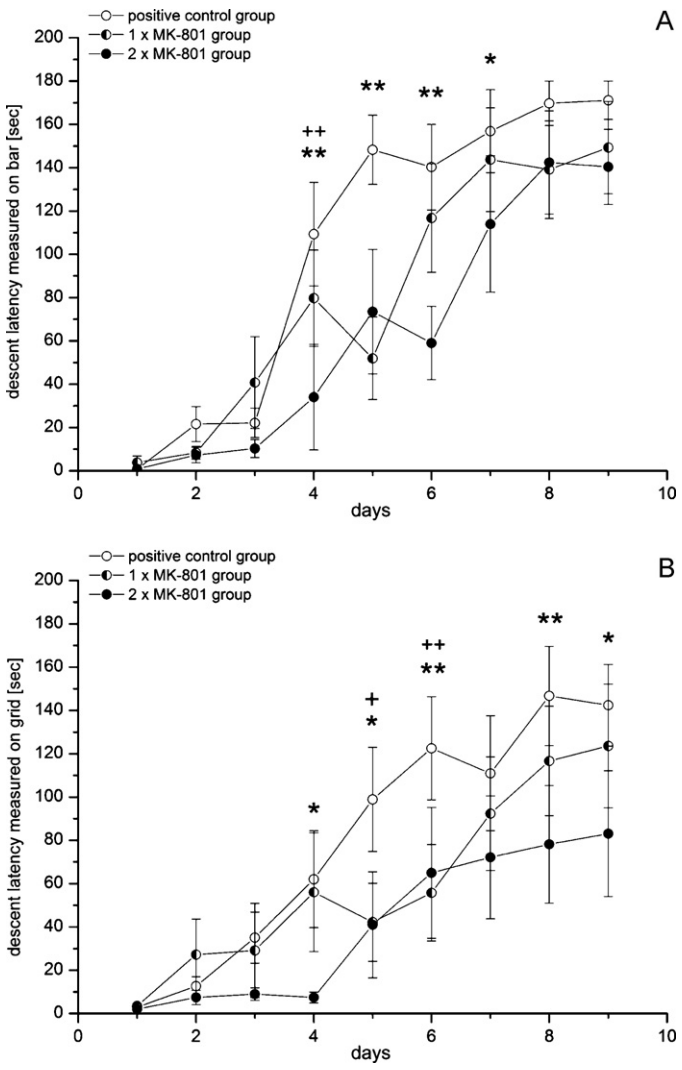

Fig. 1. Means ± SEM of descent latency after daily injection of 0.5 mg/kg haloperidol tested on bar (A) and afterwards on grid (B). Post-test treatment: MK-801 (0.1 mg/kg) was administrated either immediately after the test on the grid (half filled circles, 1× MK-801 group), or immediately after the test on the grid and 30 min later (filled circles, 2× MK-801 group). Positive control group received vehicle instead of MK-801 (open circles). Statistic: post hoc Fisher's LSD test, significant differences between the positive control and 1× MK-801 groups are marked by plus signs ($^{+}p < 0.05$ and $^{++}p < 0.01$) and differences between positive control and 2× MK-801 groups are marked by asterisks ($^{*}p < 0.05$ and $^{**}p < 0.01$).

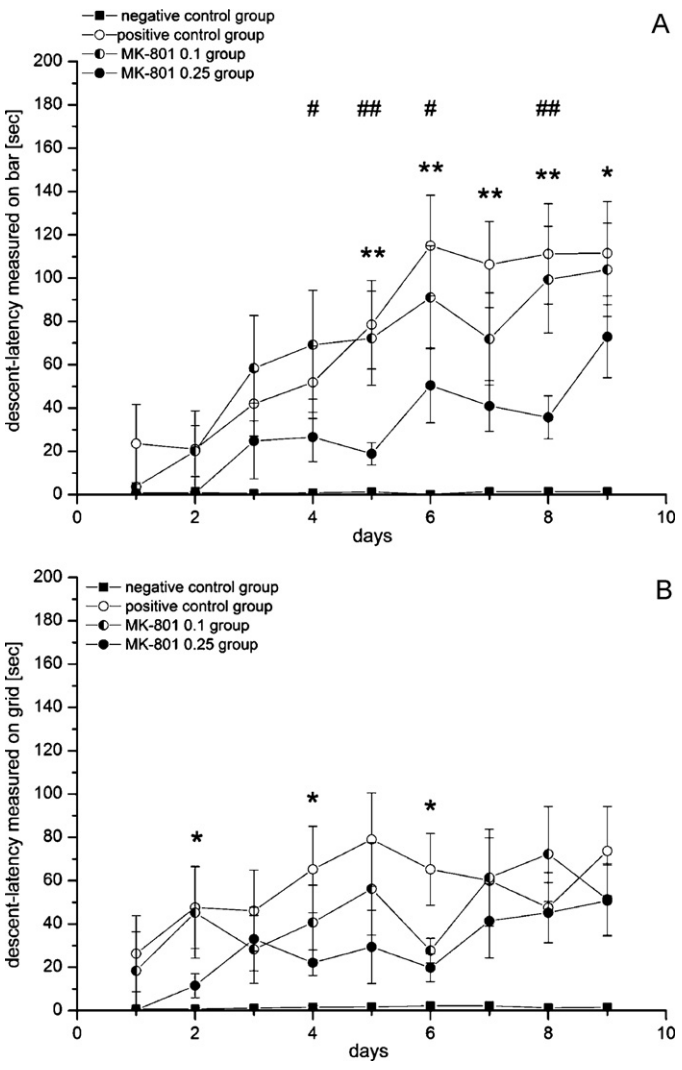

Fig. 2. Descent latency after daily injection of vehicle (rectangles) or 0.5 mg/kg haloperidol (circles) tested on bar (A) and afterwards on grid (B) displayed as means ± SEM. Post-test treatment: vehicle (rectangles, negative control group and blank circles, positive control group), 0.1 mg/kg MK-801 (half filled circles, MK-801 0.1 group) or 0.25 mg/kg MK-801 (filled circles, MK-801 0.25 group). Statistics: post hoc Fisher's LSD test, significant differences between the positive control and MK-801 0.1 groups are marked by plus signs ($^{+}p < 0.05$ and $^{++}p < 0.01$) and differences between the positive control and MK-801 0.25 groups are marked by asterisks ($^{*}p < 0.05$ and $^{**}p < 0.01$).

and a trend in reduction of decent latency due to treatment with GYKI 52466 ($F(1, 22)_{\text{treatment}} = 3.49$, $p = 0.075$). Whereas the bar test showed a strong deceleration of HIC-sensitization due to treatment with GYKI 52466, this effect was not apparent in the grid test.

4. Discussion

Post-training administration of both NMDA and AMPA/Kainate receptor antagonists decelerated the development of HIC-sensitization supporting the notion that the glutamatergic system is involved in the consolidation of this learning process.

There is substantial evidence that the ionotropic NMDA- and AMPA/Kainate-receptors are essential for both the consolidation of learning [19,21,23–25,30–33] and the development of behavioural sensitization [34–36]. Concerning NMDA receptors, a significant number of studies describe serious learning impairments due to blockade of these receptors [31,32,37]. An impairment induced by NMDA receptor antagonists was especially shown in spatial memory tasks [38,39], in visuo-spatial tasks [40], in fear conditioning [41], as well as in behavioural sensitization (reviewed in [36]). Concerning the blockade of behavioural sensitization by MK-801 most recent antagonist studies targeted the acquisition of learning. It should be noted that many learning processes develop in a state-dependent manner, i.e. the recall of stored information is possible only in the presence of a specific state which must be identical to the state during the storage of information, namely during learning [42,43]. Many substances and MK-801 explicitly do produce a strong and definite endogenous state, thus the expression of particular learned behavioural responses (like lever pressing or behavioural sensitization) can vary significantly, dependent on the state present on the test day [44,45]. Nevertheless there is most likely an involvement of NMDA receptors in sensitization development in specific and in behavioural plasticity processes in general, despite the risk of over-interpreting some results of co-administration studies. Given that MK-801 injections in our experiments were given after completion of the testing

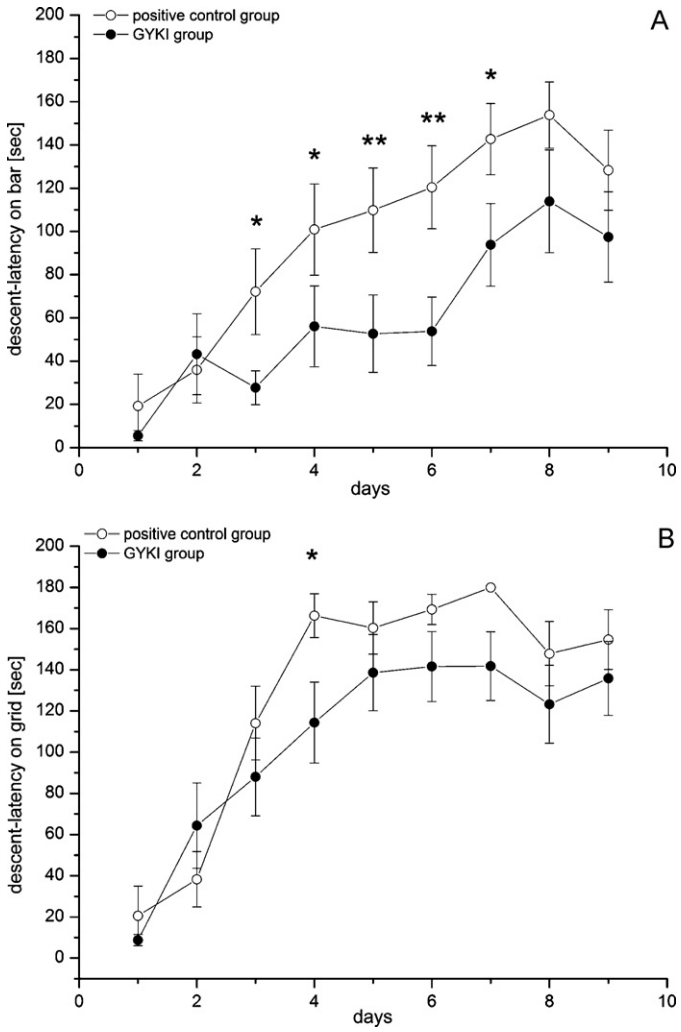

Fig. 3. Means ± SEM of descent latency after daily injection of 0.25 mg/kg haloperidol treated groups tested on bar (A) and grid (B). Post-test treatment: vehicle (blank circles, positive control group) or 5.0 mg/kg GYKI 52466 (filled circles, GYKI group). Statistics: post hoc Fisher's LSD test showed significances between both groups marked by asterisks ($^{*}p < 0.05$ and $^{**}p < 0.01$).

procedure and thus did not co-occur with haloperidol injections, we can disregard an effect of state dependency. Worth mentioning is that previous studies of our group already excluded a role of NMDA-receptors during the acquisition phase of HIC-sensitization: neither non-competitive nor competitive NMDA-receptor antagonists blocked HIC-sensitization when administered previously to the test [5,46]. However, our approach to target explicitly the consolidation phase and to avoid the acquisition phase of sensitization learning cannot fully exclude the possibility that consolidation processes start already before or during the testing. Explicit targeting of consolidation or reconsolidation by pharmacological manipulation after testing is a well established method [47–51]. In this regard it should be made clear that our hypothesis describes corticostriatal synaptic plasticity which occurs due to activation of cortical inputs to the "no-go"-medium spiny neurons and which is isochronous with the haloperidol related disinhibition of this particular neuronal population. From our perspective, the cortical activation is generated by exposure of the animals to the test apparatus in a specific context (cf. [12]). Both catalepsy testing methods (bar and grid) are accepted in the catalepsy research; however, we obtained clearer results using the bar test apparatus compared to the grid test apparatus. This might be due to the fact that there is a difference between the effort for the animals in latching onto the grid with all four paws or only holding on the bar with the forepaws, while the hind paws are lying calmly on the table surface.

An important advantage of our treatment design (i.e. to administer the glutamatergic antagonists after testing), is that we can absolutely avoid side effects of the NMDA-antagonist administration. There is a bunch of evidence that NMDA-receptor antagonists (e.g. amantadine, memantine) do possess strong therapeutic potential for the treatment of Parkinson's disease [52–56]. MK-801 which has been used in our study reduces experimental parkinsonism in numerous studies as well [57–61]. Thus, by administration of MK-801 after the test, we could avoid the acute anticataleptic effects of the substance which would have blurred the results.

It should be stated at this point, that in case of a complete blockade of the consolidation of HIC-sensitization no "absolute therapy" effect was expected. In other words, even a severe pharmacological interference with the memory consolidation process and therefore sensitization blockade would result in a stable basal catalepsy response. It is not very probable that the basal firing rate of the striatal "no-go"-neurons would decline in the presence of a D2-receptor antagonist. Nevertheless, we observe only a marginal sensitization antagonism or more correctly, a deceleration: there is a slowdown rather than a blockade of the sensitization process, since most animals reached catalepsy levels comparable to positive controls at the end of each experiment. This might have occurred for three reasons: first, the used dose of MK-801 might be insufficient for a full blockade effect. In this case, higher concentrations of MK-801 might have been effective. However, we decided to use these dosages *a priori*, in order to avoid severe adverse or neuropathological effects (cf. [62,63]. With the dose regimen in experiment 1, we assumed that the stronger deceleration of HIC-sensitization in the animal group which received MK-801 twice was due to an accumulation of MK-801 rather than due to a temporal mechanism [this interpretation is also supported by pharmacokinetics data on MK-801 [64,65]]. We hence designed our second experiment in order to assess this possibility and animals were treated once immediately after the catalepsy-test with the higher dose of 0.25 mg/kg MK-801. The results of both experiments account consequently for a dose dependent attenuation or retardation of the catalepsy. Second, the investigated glutamatergic receptors might not be the only mechanistic players within the consolidation of HIC-sensitization. This idea is supported by the absence of effects of NMDA-antagonists during the acquisition of HIC-sensitization, i.e. parts of HIC-sensitization related neuronal plasticity occurs independently of NMDA receptors [5,46]. Third, blockade of NMDA-receptors only after the test, i.e. after test-induced cortical activation, might be simply insufficient for a full blockade of the related consolidation process. Then, consequently, the consolidation process would have started already before or during testing (or at least the role of NMDA-receptors within). As already discussed above it would then not be possible to distinguish between acquisition and consolidation phases.

In the third experiment we used the selective AMPA/Kainate receptor antagonist GYKI 52466. We used a low dose as well in order to avoid severe side effects [66]. As it turned out, this dose was already effective in attenuating the consolidation of HIC-sensitization, although the effect was not strong. Interestingly, the literature search does not deliver a clear-cut antiparkinsonian effect of AMPA-receptor antagonists. Systemic administration of AMPA receptor antagonists NBQX and GYKI 52466 did not have any direct anti-cataleptic potential when tested in an acute model of haloperidol treated rats [67]. Opposite results have been observed for NBQX [68] and a co-administration of NBQX and L-DOPA [69]. In another previous study, the AMPA/Kainate receptor antagonist GYKI 52466 did not alter the HIC acutely while it significantly antagonised the MK-801 induced locomotor hyperactivity [58].

5. Conclusion

HIC-sensitization is a robust and context dependent [15] learning process. Here we ascertain that the mechanisms underlying the consolidation of HIC-sensitization differ from the mechanisms that are active during acquisition with regards to NMDA and AMPA/Kainate receptor involvement. Whereas pre-test administration of glutamate antagonists had no effect on the acquisition phase of HIC-sensitization, we show for the first time that post-test administration of a glutamate antagonist interferes with the consolidation phase and decelerates the previously proposed "no-go"-learning within basal ganglia, a learning process evidently associated with the pathophysiology of Parkinson's disease and schizophrenia [70,71]. Hence, treatment with NMDA- or AMPA/Kainate receptor antagonists might be useful not only as acute therapeutics [72] but might additionally slow down the progressive aggravation of Parkinson symptomatology. Our results further provide an important contribution to the current knowledge of basal ganglia plasticity, especially that one mechanistic element of Parkinsonism-associated "no-go" learning is (during consolidation and not acquisition) dependent on functional NMDA and AMPA/Kainate receptors.

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