Sense Oligodeoxynucleotides to GluN1 Subunit of NMDARs Improve Long-Term Potentiation Development and Protect Synaptic Activity in Anoxic Conditions

Anatoly A. Mokrushin

I.P. Pavlov Institute of Physiology, Russian Academy Science, Saint-Petersburg, Russia
Email: mok@inbox.ru

Abstract. Modifications of *N*-methyl-D-aspartate receptors (NMDARs) have been implicated in synaptic plasticity and learning in normal and pathological conditions. We studied the efficiency of synaptic plasticity - the development of the long-term potentiation/depression (LTP/LTD) in olfactory cortex slices, modifying the GluN1 subunit of NMDARs with sense or antisense oligodeoxynucleotides (ODNs). Treatment of slices with sense ODNs to GluN1 subunit enhanced LTP and acted as nootrop - piracetam. In ischemia-like conditions (severe 10 min anoxia), treatment of slices with sense ODNs protected synaptic activity and promoted the development of LTP in contrast to complete inhibition of the activity in control conditions. In practical implications such directed up-regulation of NMDARs may be taken into attention for adjusting their activity as specific target for clinic.

Keywords: Synaptic plasticity, field potentials, GluN1 subunit NMDAR

Abbreviations: ACSF, artificial cerebrospinal fluid; LOT, lateral olfactory tract; FP, field potential; EPSP, excitatory postsynaptic potential; NMDAR, N-methyl-D-aspartate receptor; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors; GluN1, subunit of the NMDA receptor; LTP/LTD, long-term potentiation/depression; ODNs, oligodeoxynucleotides.

1 Introduction

Ionotropic glutamate receptors, specifically *N*-methyl-D-aspartate receptors (NMDARs) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors (AMPARs) play a main role in excitatory neurotransmission and involve in synaptic plasticity [1]. Activity-dependent, bidirectional control of synaptic efficacy is thought to contribute in many forms of experience-dependent plasticity, including learning and memory. In the case of learning, NMDARs are known to be important for triggering learning-related plasticity; AMPARs are thought to be important for the expression of synaptic changes following the activation of the NMDA receptor [2]. The changes in NMDAR subunit composition, comprised of the essential GluN1 subunit and various GluN2 subunits, have been shown to modify synaptic plasticity [3–5]. Alterations in expression of synaptic GluN1 subunit of NMDAR are involved in the neural mechanisms underlying certain forms of learning [6, 7] and implicated in cognition dysfunctions especially in neurological disorders [8, 9]. Currently, enhancement of NMDAR function is regarded as an important goal for recovering of cognitive decline [10].

In this study we focused on the long-term LTP/LTD switch balance, modifying the level of GluN1subunit of NMDAR in olfactory cortex slices with sense or antisense oligodeoxynucleotides (ODNs). The slices provide an experimental object allowing to maintain the normal function of cellular structures for the analysis of incoming sensory input with the extracellular potentials recording. Cutting surface is located on the inside, allowing to keep the normal function of cellular structures for the analysis of incoming sensory input [11, 12]. In these brain slices the separate exciting pre-and postsynaptic NMDA and AMPA-mediated processes are reliably identified [13, 14]. Therefore, the slice preparations are very convenient for the various pharmacological tests. We have studied the influence of GluN1 subunit on the NMDAR-mediated synaptic plasticity (LTP/LTD) development in slices treated with sense and antisense ODNs. Furthermore, we have studied the influence of the ODNs treatment on synaptic activity and plasticity of NMDARs in ischemia-like conditions (10 min severe anoxia).

Copyright © 2018 Isaac Scientific Publishing

2 Materials and Methods

2.1 Animals and Slice Preparations

All animals used in this study were treated with observance of recommendations on ethics of work with the animals offered European Communities Council Direction (86/609 EEC). The experiments with rats were approved in strict accordance with the Russian Federation Council's Guide for the Care and Use of Laboratory Animals (1994) and with the guidelines of the IP Pavlov Institute Physiology Russian Academy of Sciences of the ethical code (1996). Male Wistar rats (200-250 g) were housed four per cage on a 12 h dark/light cycle in a temperature-controlled environment with free access to food and water. All efforts were made to minimize animal suffering and reduce the number of animals used.

Tangential slices of olfactory cortex about 400-500 μm in thickness prepared within 1 min were maintained in artificial cerebrospinal fluid (aCSF), consisted of (in mM): 124 NaCl, 5 KCl, 2.6 $CaCl_2$, 1.24 KH_2PO_4, 1.2 $MgSO_4$, 3 $NaHCO_3$, 10 glucose, 23 Tris-HCl (Sigma, USA); equilibrated with O_2, with osmolarity of 295-305 mOsm. The temperature was 37°C, pH 7.2-7.3.

The use of Tris-HCl allowed us to conduct the experiments in an atmosphere of O_2. Concentrations of Ca^{2+} and Mg^{2+} were optimized to retain a maximal synaptic activity in olfactory cortex for 10-12 h [12]. The automatically controlled rate of the slice perfusion along with a continuous delivery of oxygen was equal to 2 ml/min. A complete exchange of the solution in the recording chamber occurred in about 1 min.

In the series of experiments for studying the ODNs treating influence in anoxic condition, we used the replacement of oxygen supply to recording chamber with nitrogen during the slices incubation. Firstly, we compared the influence of 2, 5 and 10 min anoxia on modifications of the NMDA EPSP amplitudes in slices treated with ODNs. Then we tested the LTP/LTD distribution in slices treated with sense and antisense ODNs after 10 min anoxia.

2.2 Oligodeoxynucleotides Treatment Protocols

To test whether the treatment with ODNs targeted to specific GluN1 subunits of NMDARs could influence the LTP/LTD induction, we incubated the rat olfactory cortex slices with sense (5`-CTACAACGTACAAGTAGT -3`) or antisense (5`- CAGCAGGTGCATGGTGCT -3`) ODNs [15]. ODNs, obtained from custom-synthesized at GNC Vector (Novosibirsk, Russia), were dissolved in ACSF to 10 μM concentration.

At first, to ensure that ODNs treatment reliably led to their effects we determined the required time of the slices incubation with ODNs. We found that the incubation of brain slices with ODNs during 270 min was already sufficient to achieve their persistent and sustained effects even after washing. For greater certainty, we used a longer period of incubation – 360 min.

2.3 Electrophysiological Recordings

Electrophysiological and pharmacological identification of AMPARs and NMDARs in piriform cortex of olfactory cortex slices allowed to analyze evoked basal glutamatergic synaptic transmission and synaptic efficiency of NMDAR-dependent LTP or LTD after high frequency tetanization of the lateral olfactory tract (LOT) [12]. Briefly, the field potentials (FPs) were evoked using stimulating platinum bipolar electrodes with a tip separation of 0.5 mm positioned onto the proximal part of LOT – the main input of afferent impulses to neurons of olfactory cortex. The point of recording was located in this focus of maximal activity. Orthodromic stimulation of LOT imitated the flows of afferent impulses from the mitral neurons of the olfactory bulb *in vivo*. The rectangular pulses with duration of 0.05-0.1 msec and the intensity of 1-3 μA were evoked with aid of the constant current stimulator (ESU-1, Russia) through platinum custom-made bipolar concentric electrode insulated at the cut ends. The FPs from slices were recorded using a glass microelectrode. A tip resistance of microelectrode, filled with 1 M NaCl was 1-5 MΩ. FPs recordings were performed, using an NTO-2 amplifier (Russia). The reference silver electrode was located in a chamber floor.

 Copyright © 2018 Isaac Scientific Publishing

We analyzed the following individual components of FPs: AMPA and NMDA EPSPs with pharmacological identification as previously described [14]. FPs were recorded after stimulation with frequency 0.003 Hz during 15 min and referred as a control. Such electric stimulation was infrequent to eliminate the development of a habituation in olfactory neurons in answer to repeated stimulation.

2.4 FPs Processing

The FPs were processed in the on-line mode after amplifying (NTO-2, Russia), and then were digitized with the analog-digital converter MD-32 (Russia) (sample rate 25 kHz) and transmitted to computer for registration and subsequent analysis using special homemade software. We estimated the amplitudes of FPs components from the isoline to the peak level. The amplitudes of AMPA EPSP we assessed within a 2 msec window centered at the peak of the response. Peak NMDA EPSP was measured as the average potential observed in an 8 msec window [14]. At that time, FPs were recorded in response to electric stimulation with frequency 0.003 Hz during 15 min.

For LTP/LTD induction we employed fourfold high frequency tetanization of the LOT fibers: potentiating trains consisted of 10 sets of four pulses at 100 Hz delivered at 200 msec intervals (θ burst stimulation – TBS). It is known, that the 200 msec interval approximates the rate of exploratory sniffing in the rat, which corresponds to the limbic theta rhythm. After 5-10 min of the last tetanization the FPs were registered at the single LOT stimulation and then the NMDA-dependent LTD/LTD development was registered after LOT tetanization during 85 min. We clarified the modification of postsynaptic excitatory components of FPs, at 45 min point after TBS of LOT. For these purposes, we registered and analyzed the AMPA and NMDA EPSPs amplitudes modifications in the phase of the LTP or LTD maintenance [12].

We compared the effects of both ODNs and piracetam (2-oxo-1-pyrrolidine-acetamide) on neuroplasticity in slices taking account the possibility of nootropic-like potential of these ODNs. In these series of experiments, we estimated the LTP/LTD distributions in slices in control group; in slices treated with sense or antisense ODNs and in slices treated with 250 μM of piracetam.

2.5 Reagents

All chemical reagents and piracetam used for incubation medium were from “ChimReactive” (Russia).

2.6 Data Analysis and Statistics

Statistical comparisons were performed with nonparametric Wilcoxon–Mann–Whitney U test. Numerical data were expressed as mean ± standard error of the mean (S.E.M.). The level of statistical significance was set at $P \leqslant 0.05$.

3 Results

We revealed that the basic amplitude/temporal characteristics of NMDA EPSP in piriform cortex in response to LOT stimulation with frequency 0.003 Hz were not modified after 6 h treatment of slices with sense and antisense ODNs. On the contrary, the amplitudes of NMDA EPSP after “cognitive load” (TBS) were significantly changed depending on the type of slice treatment (NMDARs knockdown).

3.1 LTP Development after NMDAR Knockdown with Sense ODNs

We found that treatment of slices with sense ONDs actuality modulated the activity of GluN1 subunit. The NMDAR-dependent LTP was enhanced compared with control one in nontreated slices after TBS (Figure 1).

Statistical analysis of curves (a) and (b) with U pair-match criterion showed the significant differences of phases of the LTP maintenance between control slices and slices treated with sense ODNs ($U = 18$, $P \leqslant 0.05$, $n = 11$ for each point) beginning from the 10 min.

In slices treated sense ODNs, TBS led to induction of quick initial phase of NMDAR-dependent LTP. The amplitude of NMDA EPSP corresponded to this phase exceeded the control value although the

Copyright © 2018 Isaac Scientific Publishing

differences were not significant (191.0 ± 8.0% vice verse 162.0 ± 9.0%, $U = 38$, $n = 11$, $P \geqslant 0.05$) (Figure 1). The period of LTP maintenance was steady during all time of registration (85 min). The amplitudes of NMDA EPSP was significantly enhanced compared with the control values (210.0 ± 15.0% versus control 158.0 ± 9.0%, $U = 22$, $n = 11$, $P \leqslant 0.05$). It is important that the phase of LTP maintenance prolonged in the treated slices (up to 85 min), while in control slices the phase of termination of LTP was observed beginning with 70th min (Figure 1a, b).

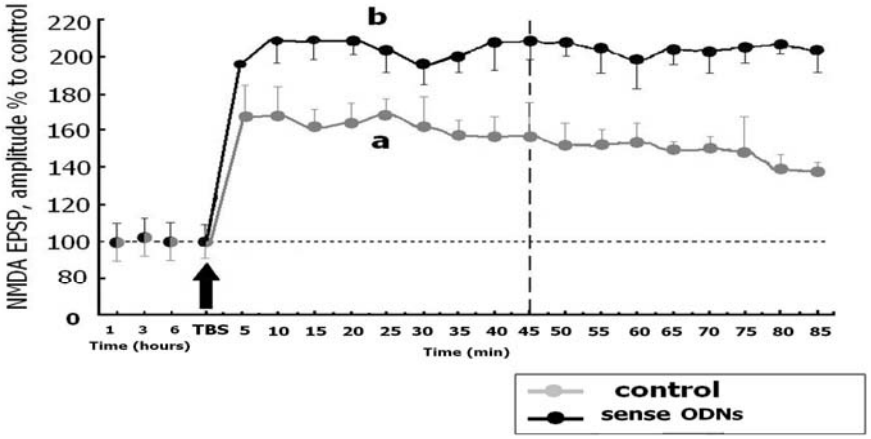

Figure 1. Induction and phase of LTP maintenance in piriform cortex of slices after NMDARs knockdown.

NMDARs-dependent LTP in control slices (a), NMDARs-dependent LTP in slices pretreated with sense ODNs to GluN1subunit (b). Horizontal dotted lines – control values of NMDA EPSP. Thick up arrow (TBS) – LOT tetanization, after 6 h of the slices incubation in ACSF for control and for pretreated with sense ODNs. Vertical dashed line at 45 min represented the FPs demonstrated in Figure 2.

3.2 Excitatory Postsynaptic Components of FPs in Piriform Cortex of Slices after Treating with Sense ODNs

We focused on the time point of 45 min corresponding to a phase of LTP maintenance (Figure 2, peak AMPA and NMDA amplitudes marked as vertical dotted lines). In control (nontreated) slices TBS resulted in significant increase of the AMPA and NMDA EPSP amplitudes (Figure 2b). We revealed that the slight increasing of latency of the maximal AMPA EPSP amplitude occurred in this time point possibly due to asynchronic activation of the AMPARs.

The NMDA EPSP amplitude the slices treated with sense ODNs has become still higher, while the amplitude of AMPA EPSP was decreased. The formation of such plateau between AMPA and NMDA components of FPs indicated that the permeability of AMPA receptors to Na^+ ions inhibited after TBS in slices treated with sense ODNs. At the same time the increase of the NMDA EPSP amplitude indicates that such treatment enhanced the permeability of NMDARs to Ca^{2+} ions thereby prolonging the time of the LTP maintenance. Taking together, these data convincingly pointed out the possibility of sense ODNs to act as cognitive enhancer.

 Copyright © 2018 Isaac Scientific Publishing

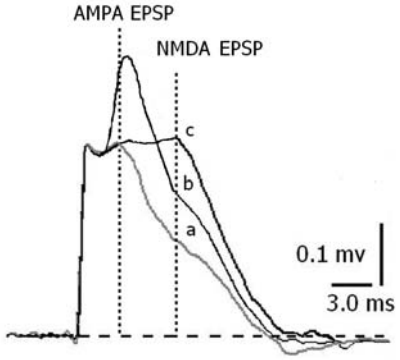

Figure 2. Extracellular FPs in piriform cortex of slices in the phase of LTP maintenance after NMDARs knockdown with sense ODNs.

FPs in control during 6 hours (a), FPs in control after 45 min TBS (phase of the LTP maintenance) (b), FPs after 45 min TBS (phase of LTP maintenance) in slices pretreated with sense ODNs (c). Each FP is the result of summation of the five consecutive responses on the orthodromic single LOT stimulation with frequency 0.003 Hz.

Horizontal dotted line – isoline, peak amplitudes of AMPA and NMDA EPSPs in control marked as vertical dotted lines. Note, right shift of AMPA and NMDA EPSPs amplitudes denoted an increasing latency of their generation in slices treated with sense ODNs. Calibration is as indicated.

3.3 LTD Development after NMDARs Knockdown with Antisense ODNs

Initial phase of the NMDAR-dependent LTD after TBS of slices treated with antisense ODNs corresponded to this phase in control (non treated slices) ($U = 48$, $n = 11$, $P > 0.05$). Similarly, the phase of LTD maintenance in slices treated with antisense ODNs was the same as control one (Figure 3).

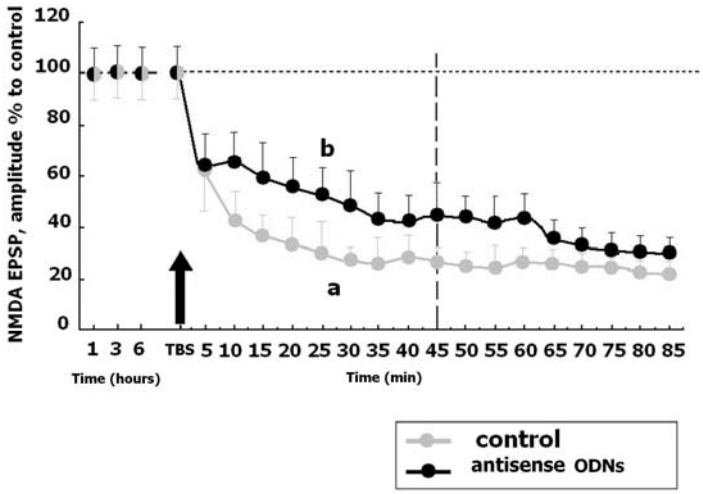

Figure 3. The LTD development in piriform cortex of slices after NMDARs knockdown.

3.4 Excitatory Postsynaptic Components of FPs in Piriform Cortex of Slices after Treatment with Antisense ODNs

NMDARs-dependent LTD in control slices (a), NMDARs-dependent LTD in slices pretreated with antisense GluN1 (b). Horizontal dotted lines – control values of the NMDA EPSP amplitudes. Thick up arrow (TBS) – LOT tetanization, after 6 h of the slices incubation in ACSF for control and for treated

Copyright © 2018 Isaac Scientific Publishing

with antisense ODNs. Vertical dashed line at 45 min represented the FPs demonstrated in Fig. 4. Note, NMDARs-dependent LTD in slices pretreated with antisense ODNs was superposable to the same of control after TBS ($U = 33$, $P \geqslant 0.05$, $n = 11$ for each point).

Compare with the FPs parameters of the control non tetanized slices, TBS induced insignificant modifications of AMPA and NMDA components of FPs both in treated with antisense ODNs and non treated slices at 45 min corresponding to the phase of LTD maintenance (Figure 4). These data indicate that treatment of slices with antisense ODNs lowered the permeability of NMDA receptors to Ca^{2+} ions, possibly acting as noncompetitive antagonist of the NMDARs.

As a result, treatment of slices with antisense ODNs did not actually affected the phases of LTD and failed to inhibit the process of LTD development.

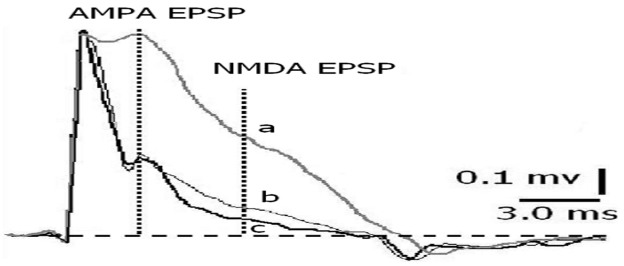

Figure 4. Extracellular FPs in piriform cortex of slices in the phase of LTD maintenance after NMDARs knockdown.

FPs in control during 6 hours (a), FPs in control after 45 min TBS (phase of the LTD development) (b), FPs after 45 min TBS (the same phase) in slices treated with antisense ODNs (c). Each FP is the result of summation of the five consecutive responses on the orthodromic LOT stimulation with frequency 0.003 Hz. Horizontal dotted line – isoline, peak amplitudes of AMPA and NMDA EPSPs in control marked as vertical dotted lines. Calibration is as indicated.

3.5 The LTP/LTD Switch Balance in Slices Treated with ODNs and Piracetam, Nootropic Drug

The LTP/LTD induction and development after TBS in control slices in piriform cortex occurred approximately in equal proportions consisting 45-47% for each form of plasticity. About 5-10% of slices had no any changes of plasticity to such TBS (Figure 5, absence of LTP/LTD induction marked as dark column). Up- and down regulation of GluN1 receptor activity in slices resulted in a redistribution of forms of plasticity manifested in slices. Thus, in slices treated with sense ODNs the LTP form was dominated, whereas the LTD form of plasticity prevailed in slices treated with antisense ODNs.

We compared these results with the LTP/LTD distribution in slices treated with piracetam. Piracetam, a derivative of the neurotransmitter gamma-aminobutyric acid (2-oxo-1-pyrrolidine-acetamide) is the most common of the nootropic drugs. To date, piracetam improves learning, memory, brain metabolism [16]. In our study the effect of sense ODNs on LTP/LTD distribution was identical to the effect of pirecetam. This form of plasticity was dominantly found in the majority of slices (Figure 5). It may be concluded, that sense ODNs acted like piracetam improving the LTP development. On the contrary, the antisense ODNs treatment led mainly to development of the LTD form in slices. Thus, the LTP/LTD distribution was shifted to prevalence of depressive form of plasticity involving the majority of synaptic transmissions.

 Copyright © 2018 Isaac Scientific Publishing

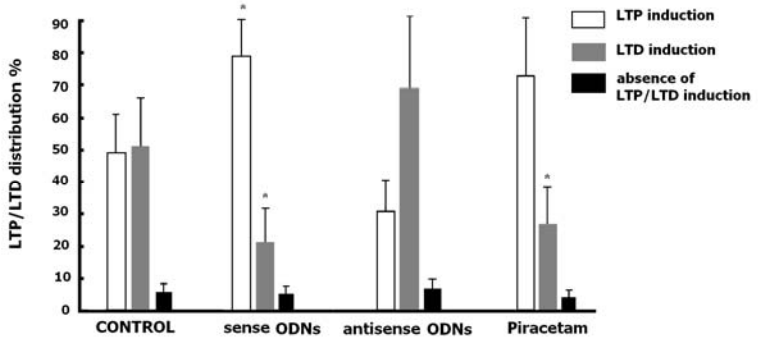

Figure 5. Development NMDARs-dependent LTP/LTD in piriform cortex of slices under action nootrop piracetam (250 μM), sense ODNs and antisense ODNs (10 μM).

3.6 Activity of NMDARs and Modifications of Synaptic Plasticity in Slices after NMDARs Knockdown in Anoxic (Ischemia-like) Conditions

In other series of experiments we tested the up- and down GluN1 regulation in slices under anoxia influence. The axis of ordinates – distribution, % of LTP and LTD from the total number of the tested slices as well as slices without synaptic plasticity (absence of LTP/LTD induction). * – $P \leqslant 0.05$. $n = 21$ (control), $n = 8$ (piracetam), $n = 12$ (for sense and antisense ODNs).

For these purposes, we used the model of anoxia *in vitro*. We compared the modifications of the NMDA component of FPs in treated with ODNs and in control (non treated) slices in different periods of anoxic exposure. The twofold increase of the NMDA EPSP amplitudes was found in control slices after 2 min anoxia. Then, after 5 min of anoxia a sharp decreasing of the NMDA EPSP amplitude occurred. Following 10 min anoxia led to irreversible complete blockade of the NMDARs activity and the subsequent reoxygenation failed to restore the amplitude of NMDA EPSP in control slices. On the contrary, treatment with sense ODNs promoted the maintenance of synaptic activity in slices under 2 and 5 min anoxia and furthermore in conditions of severe anoxia (Figure 6A).

The synaptic plasticity was not revealed in control slices under 10 min anoxia after TBS. On the contrary, in slices treated with sense or antisense ODNs in spite of severe anoxic impact, the LTP and LTD were actually developed (Figure 6B). It is important, that treatment with sense ODNs promoted retention of synaptic plasticity and the distribution of LTP/LTD in slices was in the same proportion, as in control, while antisense ODNs promoted mainly the LTD induction.

4 Discussion

Our data have shown that the NMDAR-dependent LTP form of synaptic plasticity readily developed and enhanced in piriform cortex of slices treated with sense ODNs. Likewise, the number of slices which manifested preferentially LTP form of learning was increased after such treatment. It may be explained by an effect of cognitive enhancement. Moreover, synaptic activity of NMDARs in slices treated with sense ODNs as well as synaptic plasticity was preserved in anoxic (ischemia-like) conditions.

Long-term synaptic changes such as synaptic plasticity and memory formation are associated with activation of glutamatergic synapses through the NMDA receptor channels [1, 17, 18]. The mechanism of the glutamate receptor ion channels activity depends on their assembly, activation and modulation [19]. The NMDARs subunit composition and location are major determinants of glutamatergic postsynaptic properties [20, 21]. Modifications in NMDARs, are involved in alterations of synaptic plasticity as no associative form of learning, LTP and LTD, as well as more complex forms [3–7, 22]. Rapid forms of NMDAR trafficking and its surface distribution may also regulate plasticity and modulate cognitive abilities [23–26]. GluN1 subunit plays a main role in NMDARs functioning as an obligatory receptor subunit for channel function [1] and widely expressed in CNS [27–29], involving in neuronal plasticity, learning, and memory [9, 30–32].

Copyright © 2018 Isaac Scientific Publishing

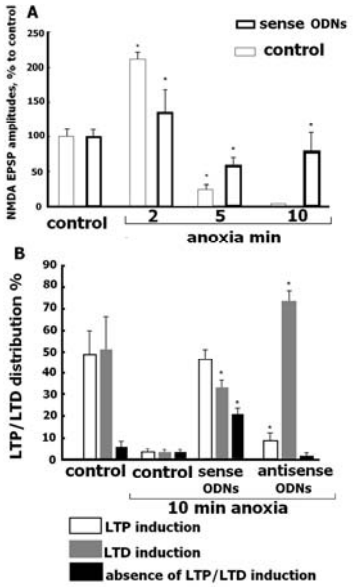

Figure 6. Effects of anoxia on the activity of NMDARs (A) and on the plastic modifications in piriform cortex of slices after NMDARs knockdown (B).

A, time points - 2, 5 and 10 min anoxia, the modifications of the NMDA EPSP amplitudes in control slices and in slices treated with sense ODNs. * $P \leqslant 0.05$, $n = 9$ (control), $n = 4$ (for sense ODNs). B, distribution, % of LTP and LTD from the total number of the tested slices as well as slices without synaptic plasticity (absence of LTP/LTD induction) after exposure to 10 min anoxia. * $P \leqslant 0.05$, $n = 11$ (control), $n = 5$ (sense ODNs), $n = 4$ (antisense ODNs). Note, treatment of the slices with sense ODNs preserves the synaptic plasticity in conditions of severe anoxia. In slices treated with antisense ODNs the synaptic plasticity after 10 min anoxia also maintained but the LTD form was dominated.

Our data revealed that treatment of brain slices with sense ODNs induced significant transformation in NMDARs. The important functional implications of GluN1subunit of NMDAR in the rat piriform cortex consisted in its modulating influence on LTP/LTD development. Up regulation of NMDAR in slices induced by treatment with sense ODNs have resulted in enhancing of the NMDA-dependent LTP. GluN1 knockdown with antisense ODNs slightly influenced NMDA-dependent LTD. We supposed that such pharmacological processing resulted in improving of synaptic conductivity and eventually to facilitation of learning. It is concordant with a present understanding of the NMDARs functions [10].

We estimated the number of slices which manifested LTP or LTD after treatment with sense and antisense ODNs. We showed that treatment of slices with sense ODNs modulates the processes of learning, so that a large number of slices demonstrated the LTP form of plasticity. Treatment of slices with antisense ODNs differently affected the synaptic plasticity. The predominance of the LTD form was observed. Having established such cognitive-associated enhancing of LTP induced by sense ODNs, we compared this effect with the same of piracetam in our conditions. As it was shown, piracetam (10^{-6} to 10^{-4}) M, the most common of the nootropic drugs, augmented the LTP in the CA3 region of guinea pig hippocampal slices [33] like the other drug structurally related to piracetam in mouse hippocampal and olfactory slices [34]. Piracetam application elevated density of NMDAR and normalizes their enhanced affinity to glutamate [35]. In our study, treatment of slices with sense ODNs strengthened the activity of NMDARs, such nootropic-like effects were identical to those of piracetam. Implications of GluN1 subunit in regulation of synaptic plasticity determined in our study demonstrate that sense ODNs may enhance non-associative form of the learning in piriform cortex acting as cognitive enhancer.

It is known, that inappropriate NMDARs activation is involved in the etiology of several diseases including acute insults [36, 37] and epilepsy [38]. GluN1 subunit hypofunction is possibly connected with cognition defects [39]. We examined the role of up- and down regulation of GluN1 in conditions of anoxia.

 Copyright © 2018 Isaac Scientific Publishing

It was established, that brain slices are very sensitive to insufficient oxygen supply *in vitro* [40]. Previously, we showed that anoxia during 2 min led to activation of NMDARs. Whereas subsequent severe 10 min anoxia induced irreversible disturbances in NMDARs-mediated synaptic activity [41, 42]. In present study the treatment of slices with sense (not with antisense) ODNs protected the activity of NMDARs in the conditions of severe anoxia. The amplitude of NMDA EPSP in treated slices was similar to non-anoxic control. Moreover, the LTP/LTD distribution in slices treated with sense ODNs resembled the control one, it may be associated with protective effect of the ODNs treatment.

5 Conclusion

The induction and development of LTP and LTD in olfactory cortex slices depends on the modification of GluN1 subunits with sense or antisense ODNs. The treatment of slices with sense ODNs causes a shift in the balance of LTP/LTD in the predominance of LTP similar to the effect of piracetam. Up regulation of GluN1 subunit of NMDARs promotes the preservation of NMDARs synaptic plasticity in ischemia-like conditions. Such pharmacological optimization of activity of NMDARs via modulation of GluN1 subunit may provide an effective approach for improving of cognitive functions in normal and ischemic conditions. Therefore, in practical implications a capability of sense ODNs to modulate the NMDARs-mediated synaptic plasticity should be taken into attention for coordination of the receptor activity as specific target in cure of cognitive processes in normal and pathological conditions.

Conflict of interest. The author states that he has no financial, religious and other conflicts of interest. The author is responsible for the content and writing of the article.

Acknowledgments. The authors thank Mrs. Galina Smirnova for her excellent technical assistance.

References

1. S.E. Traynelis, P.W. Lonnie, J.Mc.B. Chris, S.M. Frank, M.V. Katie, K.O. Kevin, B.H. Kasper, Y. Hongjie, J.M. Scott, and D. Ray, “Glutamate receptor ion channels: structure, regulation, and function”. Pharmacology Review, vol. 62, pp. 405–496, 2010.
2. N. Rebola, B.N. Srikumar, and C. Mulle, “Activity-dependent synaptic plasticity of NMDA receptors.” Journal Physiology, vol. 588, pp. 93–99, 2010.
3. S.G. Cull-Candy, and D.N. Leszkiewicz, “Role of distinct NMDA receptor subtypes at central synapses”. SciSTKE, vol. 255, pp. re16, 2004.
4. M.H.Ulbrich, and E.Y. Isacoff, “Rules of engagement for NMDA receptor subunits.” PNAS, vol. 105, pp. 14163–14168, 2008.
5. C.L. Salussolia, M.L.Prodromou, P. Borker, and L.P. Wollmuth, “Arrangement of subunits in functional NMDA receptors.” Journal Neuroscience, vol 31, pp. 11295–11304, 2010.
6. M. Cammarota, M.L. de Stein, G. Paratcha, L.R. Bevilaqua, I. Izquierdo, J.H. Medina, “Rapid and transient learning-associated increase in NMDA NR1 subunit in the rat hippocampus.” Neurochemistry Research, vol. 25, pp. 567–572, 2000.
7. C. Bellone, and R.A. Nicoll, “Rapid bidirectional switching of synaptic NMDA receptors.” Neuron, vol. 55, pp. 779–785, 2007.
8. S.S. Mahajan, K.H. Thai, K. Chen, and E. Ziff, “Exposure of neurons to excitotoxic levels of glutamate induces cleavage of the RNA editing enzyme, adenosine deaminase acting on RNA 2, and loss of GLUR2 editing.” Neuroscience, vol. 25, pp. 305–315, 2011.
9. A. Wright, and B.Vissel, “The essential role of AMPA receptor GluR2 subunit RNA editing in the normal and diseased brain.” Frontier Molecular Neuroscience, vol. 5, pp. 34, 2012.
10. G.L. Collingridge, A. Volianskis, N. Bannister, G. France, L. Hanna, M. Mercier, P. Tidball, and G. Fang,“The NMDA receptor as a target for cognitive enhancement.”Neuropharmacology, vol. 64, pp.13–26, 2013.
11. A.A. Mokrushin, and N.A. Emelyanov, “Effects of melanostatine (MIF-1) on focal potentials in slices of rat brain cortex.” Neuropeptides, vol. 20, pp. 87–94, 1991.

Copyright © 2018 Isaac Scientific Publishing

12.A.A. Mokrushin, “Peptide-dependent mechanisms of neural plasticity in olfactory cortex slices,”Dissertation Doctor Sciences, Pavlov Institute Physiology Russian Academy of Sciences, Saint-Petersburg, Russia, 1997. pp. 1-341.
13.A.Kh. Khama-Murad, and A.A.Mokrushin, “Stable hypertension modifies glutamatergic and GABA-ergic synaptic transmission in the rat olfactory brain cortex in vitro.” Doklady Biological Science, vol. 418, pp. 1–4, 2007.
14.A. Mokrushin, and L. Pavlinova, “Hsp70 promotes synaptic transmission in the brain slices damaged by the contact with blood clot.” European Journal Pharmacology, vol. 677, pp.55–62, 2012.
15.C. Wahlestedt, E. Golanov, S.Yamamoto, F. Yee, H. Ericson, H.Yoo, C.E. Inturrisi, D.J. Reis, “Antisense oligodeoxynucleotides to NMDA-R1 receptor channel protect cortical neurons from excitotoxicity and reduce focal ischaemic infarctions.” Nature, vol. 363, pp. 260–263, 1993.
16.K. Winnicka, M. Tomasiak, and A. Bielawska, “Piracetam an old drug with novel properties?” Acta Polish Pharmacology, vol. 62, pp. 405–409, 2005.
17.B.L. Bloodgood, and B.L. Sabatini, “ Regulation of synaptic signaling by postsynaptic, non-glutamate receptor ion channels.” Journal Physiology, vol. 586, pp. 1475–1480, 2008.
18.A. Citri, and R.C. Malenka, “Synaptic plasticity: multiple forms, functions, and mechanisms.” Neuropsychopharmacology, vol. 33, pp. 18–41, 2008.
19.M.L. Mayer, “Structure and mechanism of glutamate receptor ion channel assembly, activayion and modulation.” Current Opininium Neurobiology, vol. 21, pp. 283–290, 2011.
20.S. Lei, and C.J. McBain, “Distinct NMDA receptors provide differential modes of transmission at mossy fiber-interneuron synapses.” Neuron, vol. 33, pp. 921–933, 2002.
21.G. Kohr, “NMDA receptor function: subunit composition versus spatial distribution.” Cell Tissue Research, vol. 326, pp. 439–446, 2006.
22.L. Liu, T.P. Wong, M.F. Pozza, K. Lingenhoehl, Y. Wang, M. Sheng, Y. Auberson, and Y.T.Wang, “Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity.” Science, vol. 304, pp. 1021–1024, 2004.
23.A. Triller, and D. Choquet, “Surface trafficking of receptors between synaptic and extrasynaptic membranes: and yet they do move!” Trends Neuroscience, vol. 28, pp. 133–139, 2005.
24.C. Kopp, F. Longordo, and A. Lüthi, “Experience-dependent changes in NMDA receptor composition at mature central synapses.” Neuropharmacology, vol. 53, pp. 1–9, 2013.
25.L. Bard, and L. Groc, “Glutamate receptor dynamics and protein interaction: lessons from the NMDA receptor.” Molecullar Cell Neuroscience, vol. 48, pp. 298–307, 2011.
26.L.Ladépêche, J.P.Dupuis, and L. Groc, “Surface trafficking of NMDA receptors: Gathering from a parther to another.” Seminar Cell Development Biology, pii: S1084-9521(13)00110–00119.
27.W.X. Zhong, Z.F.Dong, M. Tian, J. Cao, L. Xu, and J.H. Luo, “N-methyl-D-aspartate receptor-dependent long-term potentiation in CA1region affects synaptic expression of glutamate receptor subunits associated proteins in the whole hippocampus.” Neuroscience, vol. 141, pp. 1399–1413, 2006.
28.V. A. Alvarez, D.A. Ridenour, and B. L. Sabatini, “ Distinct structural and ionotropic roles of NMDA receptors in controlling spine and synapse stability,” Journal Neuroscience, vol. 27, pp. 7365–7376, 2007.
29.P.F.Simòes, A.P. Silva, F.C. Pereira, E.Marques, S. Grade, N. Milhazes, F. Borges, C.F. Ribeiro, and T.R. Macedo, “Methamphetamine induces alterations on hippocampal NMDA and AMPA receptor subunit levels and impairs spatial working memory.” Neuroscience, vol. 150, pp. 433–441, 2007.
30.J. Kaur, R. Keesey, B. Magrys, H. Liu, and L.K. Friedman, “NR1 knockdown reveals CA1 injury during a developmental period of high seizure susceptibility despite reduced seizure activity.” Neuromolecular Medicine, vol. 9, pp. 298–314, 2007.
31.D.H. Youn, G. Royle, M. Kolaj, B. Vissel, and M. Randić,“Enhanced LTP of primary afferent neurotransmission in AMPA receptor GluR2-deficient mice.” Pain, vol. 136, pp. 158–167, 2008.
32.A.J. Milnerwood, C.M. Gladding, M.A. Pouladi, A.M. Kaufman, R.M. Hines, J.D.Boyd, R.W. Ko, O.C. Vasuta, R.K. Graham, M.R. Hayden, T.H. Murphy, and L.A. Raymond, “Early increase in extra synaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice.” Neuron, vol. 65, pp. 178–190, 2010.

 Copyright © 2018 Isaac Scientific Publishing

33.M. Satoh, K. Ishihara, and H. Katsuki, “Different susceptibilities of long-term potentiations in CA3 and CA1 regions of guinea pig hippocampal slices to nootropic drugs.” Neuroscience Letters, vol. 93, pp. 236–241, 1988.
34.S. Moriguchi, T. Tanaka, H. Tagashira, T. Narahashi, and K. Fukunaga, “Novel nootropic drug sunifiram improves cognitive deficits via CaM kinase II and protein kinase C activation in olfactory bulbectomized mice.” Behavior Brain Research, vol. 242, pp. 150–157, 2013.
35.S.A. Cohen, and W.E. Müller, “Effects of piracetam on N-methyl-D-aspartate receptor properties in the ageds mouse brain.” Pharmacology, vol. 47, pp. 217–222, 1993.
36.R. Machaalani, and K.A. Waters, “Distribution and quantification of NMDA R1 mRNA and protein in the piglet brainstem and effects of intermittent hypercapnic hypoxia (IHH).” Brain Research, vol. 951, pp. 293–300, 2002.
37.H. Cui, A. Hayashi, H.S. Sun, M.P. Belmares, C. Cobey, T. Phan, J. Schweizer, M.Salter, Y.T.Wang, R.A. Tasker, and D. Garman, “PDZ protein interactions underlying NMDA receptor-mediated excitotoxicity and neuroprotection by PSD-95 inhibitors.” Journal Neuroscience, vol. 27, pp. 9901–9915, 2007.
38.C.T. Toro, J.E. Hallak, J.S. Dunham, J.P. Leite, A.C. Sakamoto, R. Guarnieri, V. Fong, and J.F. Deakin, “The NR1 N-methyl-D-aspartate subunit and brainderived neurotrophic factor in temporal lobe epilepsy hippocampus: a comparison of patients with and without coexisting psychiatric symptoms.” Epilepsia, vol. 48, pp. 2352–2356, 2007.
39.E.J. Weeber, and L.D. Sweatt, “Molecular neurobiology of humanmcognition.” Neuron, vol. 33, pp. 845–848, 2002.
40.D.G. MacGregor, M.V.Avshalumov, and M.E. Rice, “Brain edema induced by in vitro ischemia: causal factors and neuroprotection.” Journal Neurochemistry, vol. 85, pp. 1402–1411, 2003.
41.M.O. Samoĭlov, and A.A. Mokrushin, “Peptide modulation of synaptic plasticity induced by anoxia. “Doklady Akademy Nauk, vol. 357, pp. 565–567, 1997.
42.M.O. Samoĭlov, and A.A. Mokrushin, “The role of endogenous neuromodulator peptides in enhacement of the functional tolerance of brain neurons to anoxia.” Bulluten Eksperimental Biolology Medicine, vol. 125, pp. 503–505, 1998.

Copyright © 2018 Isaac Scientific Publishing