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Research Report

NMDA modulation of GABA transporter current in carp retinal horizontal cells

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ABSTRACT

In the present study, the modulatory effect of NMDA on GABA transporter current was investigated on enzymatically isolated horizontal cells of carp retina. After application of NMDA (0.1 mM) for 50 s, the GABA transporter current elicited by GABA (1 mM) was decreased to 78.07±3.10% (n=5) of the control level. When the extracellular Ca^{2+} was removed from the Ringer's solution, the NMDA inhibitory effect on the GABA transporter current was eliminated. The suppression effect could be attenuated when the Ca^{2+} release and Ca^{2+} uptake of intracellular Ca^{2+} store were blocked after the cell had been pre-incubated with 20 μM ryanodine plus 2 μM thapsigargin. Application of 10 mM BAPTA in intracellular solution also suppressed the NMDA modulation of GABA transporters. These results suggest that the activation of NMDA receptors inhibits GABA transporter-mediated current by affecting Ca^{2+} processes in the retinal horizontal cells.

1. Introduction

Horizontal cells are the interneurons in the outer retina, which are directly postsynaptic to photoreceptors. These cells are responsible for the regulation of the output properties of photoreceptors, as well as the formation of the antagonistic surround receptive field property of the retinal bipolar cells and ganglion cells (Mangel, 1991). γ-aminobutyric acid (GABA) is the neurotransmitter released by luminosity-type (L-type) cone-driven horizontal cells, and has been hypothesized to play a role in creating the surround portion of the classic center-surround receptive fields of retinal neurons. GABA transporters on the horizontal cells are responsible for GABA uptake and release in reverse modes (Yazulla and Kleinschmidt, 1983; Yazulla, 1985).

N-methyl-D-aspartate (NMDA) receptors widely exist in the central nervous system, which are responsible for the regulation of excitability, as well as modulation of a variety of ion channels of neurons (Davis and Linn, 2003; Xu et al., 2005). Regulation of cytoplasmic free Ca^{2+} concentration is involved in the above processes. Recently, it was reported that functional NMDA receptors are expressed in carp retinal horizontal cells (Shen et al., 2006), but the relevant functions of NMDA receptors in the horizontal cells are not fully understood. AMPA receptors in horizontal cells mediate signal transmission from photoreceptors to horizontal cells and modulate the activity of GABA transporters in horizontal cells (Kreitzer et al., 2003; Yang, 2004). We consequently explored whether activation of NMDA receptors on horizontal cells could also alter the activity of GABA transport in these cells.

In the present work, the modulatory effect that the NMDA receptor conductance exerts on GABA transport-mediated current was investigated in freshly dissociated horizontal cells of the carp retina using patch clamp technique. The application of exogenous NMDA inhibited the activity of GABA transporters by regulating the intracellular free Ca^{2+} concen-

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tration. The inhibitory effect was attenuated when extracellular Ca^{2+} was removed or Ca^{2+} release/uptake of the intracellular Ca^{2+} store was blocked. The suppression effect could also be eliminated when the intracellular Ca^{2+} changes were attenuated by application of 10 mM BAPTA in the intracellular solution. These results indicate that the activation of NMDA receptors down-regulates the GABA transporter current by affecting the Ca^{2+} processes, including Ca^{2+} influx across the plasma membrane which is followed by Ca^{2+}-induced-Ca^{2+}-release from the intracellular Ca^{2+} store.

2. Results

In our experiments, whole-cell recordings were performed on isolated H1 horizontal cells (Fig. 1) which were voltage-clamped at –60 mV. Although application of GABA could elicit ionotropic GABA receptor-mediated and GABA transporter-mediated currents in H1 cells (Paik et al., 2003), GABA transporter current can be measured by co-application of exogenous GABA and picrotoxin (PTX, a potent antagonist of $GABA_A$ and $GABA_C$ receptors), and this GABA transporter current can be effectively suppressed by application of SKF-89976-A (Takahashi et al., 1995).

2.1. *NMDA modulation of GABA transporters*

It was recently reported that NMDA receptors are expressed in carp H1 cells (Shen et al., 2006). To analyze the possible modulatory effect that NMDA receptors exert on GABA transporters, PTX at a concentration of 300 μM was applied to block the ionotropic GABA receptors, and GABA at a concentration of 1 mM was given after the pre-application of 100 μM NMDA. In the example presented in Fig. 2A, application of GABA in the presence of PTX elicited an inward current of 182.1 pA when the cell was voltage-clamped at –60 mV, which was taken as a control. Then 100 μM NMDA was superfused for 50 s. After NMDA was washed out by the Ringer's solution for 5 s, GABA (1 mM) was applied again. The pre-application of

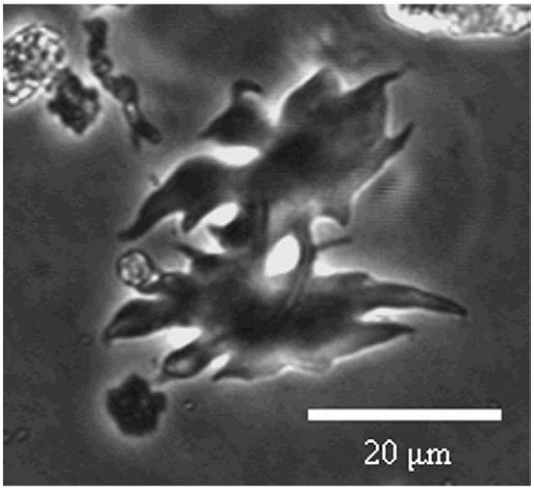

Fig. 1 – Photomicrograph of two freshly isolated retinal horizontal cells (H1 cells).

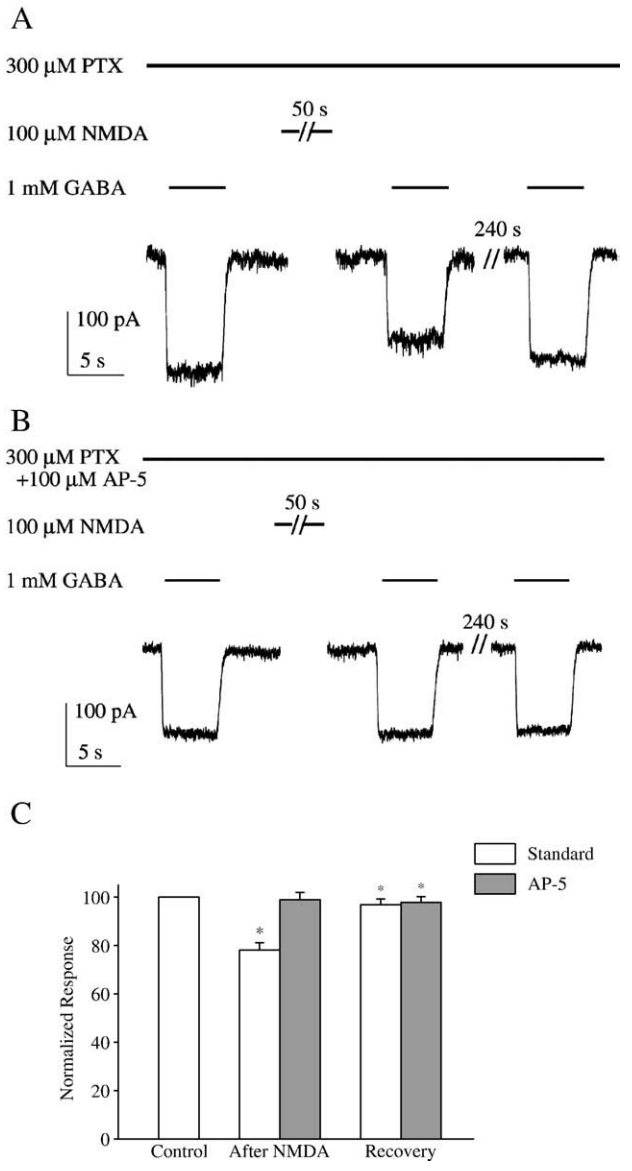

Fig. 2 – (A) An example of the GABA transporter currents measured during control, 5 s after cessation of NMDA and recovery. (B) The GABA transporter currents measured in the presence of AP-5. (C) The statistics for the GABA transporter currents (normalized against control) measured during control, 5 s after cessation of NMDA application, and recovery. White columns and grey columns represent the data collected in PTX-containing Ringer's solution and in the presence of AP-5, respectively (mean ± SD, 5 cells for each condition). *$p < 0.05$ (paired *t*-test, as compared to control).

NMDA decreased the GABA-elicited current to 136.8 pA. After superfusion with the PTX-containing Ringer's solution for another 4 min, the GABA-elicited current was mostly recovered (174.6 pA). The white columns in Fig. 2C represent the normalized responses obtained from 5 H1 cells. The GABA transporter-mediated response was decreased to 78.07 ± 3.10% (mean ± SD) of the control level after the pre-application of NMDA ($p < 0.05$, paired *t*-test), whereas the GABA-initiated response was recovered to 98.81 ± 2.38% (mean ± SD) of the

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control level ($p<0.05$, paired t-test) after the PTX-containing Ringer's solution was applied for another 4 min. The recovery was significant, although it was not complete.

To further confirm that NMDA receptors take part in the modulation of GABA transporter function, an NMDA receptor blocker, AP-5 at a concentration of 100 μM, was added into the PTX-containing Ringer's solution. Fig. 2B gives an example. It is shown that in the presence of AP-5, the GABA transporter currents were 138.8 pA, 140.9 pA, and 138.2 pA (control, after the pre-application of NMDA and recovery, respectively). The grey columns in Fig. 2C illustrate the AP-5 effect, which show that in the presence of 100 μM AP-5, pre-application of NMDA failed to induce any significant change in the GABA transporter current. The averaged GABA transporter current recorded after NMDA application was 98.93±1.63% (mean±SD) of the control level ($p>0.05$, paired t-test); and the current measured after another 4 min Ringer's wash-out was 97.78±1.73% (mean±SD) of the control level ($p<0.05$, paired t-test).

To describe the relationship between the GABA (1 mM) transporter current suppression and the concentration of NMDA applied, the dose-dependent modulatory effect is presented in Fig. 3. Different levels of NMDA (1 μM, 10 μM, 30 μM, 100 μM, 1000 μM, and 3000 μM) respectively decreased the GABA transporter currents (measured from 5 H1 cells) to 99.56±1.10%, 97.06±2.30%, 85.36±3.00%, 78.07±3.10%, 66.30±1.80%, and 65.11±1.67% (mean±SD) of the control level. The averaged data were well fitted by the curve described by $R=(100\%-R_{min})/[1+(IC_{50}/NMDA)^n]$, with R_{min} being 65.11%, IC_{50} being 47.89 μM, and n being 1.23.

2.2. Ca^{2+} processes and the NMDA receptor-mediated modulation of GABA transporters

Since NMDA receptors are Ca^{2+}-permeable (Ozawa et al., 1998), extracellular Ca^{2+} was removed from the Ringer's solution to investigate whether NMDA receptor-initiated Ca^{2+} influx was necessary for the NMDA receptor-mediated modulation of GABA transporters. Fig. 4A gives an example. The GABA transporter currents recorded from this cell were 143.3 pA, 138.6 pA, and 136.5 pA (control, after NMDA pre-application and recovery, respectively). The grey columns in Fig. 4D represent the averaged responses from 5 H1 cells in the Ca^{2+}-free Ringer's solution. The GABA transporter current recorded after NMDA (100 μM) pre-application was 97.95±2.71% (mean±SD) of the control level ($p>0.05$, paired t-test). This change was not significant. The NMDA-mediated modulatory effect was clearly attenuated in the Ca^{2+}-free Ringer's solution as compared to that during normal Ringer's perfusion as shown in Fig. 2C ($p<0.05$, unpaired t-test, comparison between the middle white column and the middle grey column in Fig. 4D). The recovery current of H1 cells in Ca^{2+}-free Ringer's solution was 96.11±2.81% (mean±SD) of the control level ($p<0.05$, paired t-test).

The activation of NMDA receptors can cause Ca^{2+}-induced-Ca^{2+}-release (CICR) from endoplasmic reticulum. To further examine the contribution of CICR in the NMDA receptor-initiated GABA transporter inhibition, 20 μM ryanodine (a ryanodine receptor inhibitor, see Sutko et al., 1997) together with 2 μM thapsigargin (a selective blocker of endoplasmic reticulum Ca^{2+}-ATPase, see Thastrup et al., 1990, Kachoei et al., 2006) were presented in the bath solution 3 min prior to the experimental recordings. Fig. 4B gives an example from a cell, in which the GABA transporter-mediated currents were 76.9 pA, 70.3 pA, and 75.1 pA (control, after NMDA pre-application and recovery, respectively). The black columns in Fig. 4D represent the normalized responses obtained from 5 H1 cells in which Ca^{2+}-release and Ca^{2+}-uptake of the intracellular Ca^{2+} store were both blocked. After pre-application of 100 μM NMDA, the GABA transporter current was decreased to 91.28±2.46% (mean±SD) of the control level ($p<0.05$, paired t-test). The degree of inhibition was remarkably attenuated as compared to that measured in the normal Ringer's solution ($p<0.05$, unpaired t-test, comparison between the middle white column and the middle black column in Fig. 4D). The recovery level was 97.66±2.16% (mean±SD) of the control level ($p<0.05$, paired t-test).

The modulatory effect of NMDA on GABA transporters via either NMDA receptor-initiated Ca^{2+} influx or Ca^{2+}-release from intracellular Ca^{2+} stores is mediated by an increase of intracellular Ca^{2+}. To examine the importance of intracellular Ca^{2+} changes, BAPTA at a concentration of 10 mM was added in the Ca^{2+}-free intracellular solution to attenuate the intracellular Ca^{2+} changes of the retinal horizontal cells. After achieving the whole-cell configuration, the retinal horizontal cell was loaded with BAPTA by diffusion from the patch pipette for 5 min. Fig. 4C gives an example from a cell, in which the GABA transporter currents were measured 109.2 pA, 107.1 pA, and 108.3 pA (control, after NMDA pre-application and recovery, respectively). The striped columns in Fig. 4D represent average responses from 5 H1 cells with 10 mM BAPTA in intracellular solution. After pre-application of 100 μM NMDA, the GABA transporter current was decreased to 96.86±1.83% (mean±SD) of the control level ($p<0.05$, paired t-test). The reduction of GABA transporter currents after pre-application of NMDA were significantly attenuated as compared to that measured with normal intracellular solution ($p<0.05$, unpaired t-test, comparison between the middle white column and the middle striped column in Fig. 4D). The

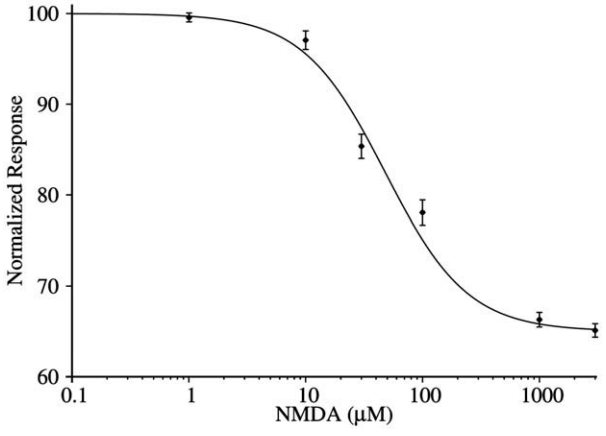

Fig. 3 – The dose–response relationship for the NMDA modulation of the GABA transporter current (1 mM GABA). The averaged data (mean±SD, $n=5$ for each) were well fitted by the curve described by $R=(100\%-R_{min})/[1+(IC_{50}/NMDA)^n]$.

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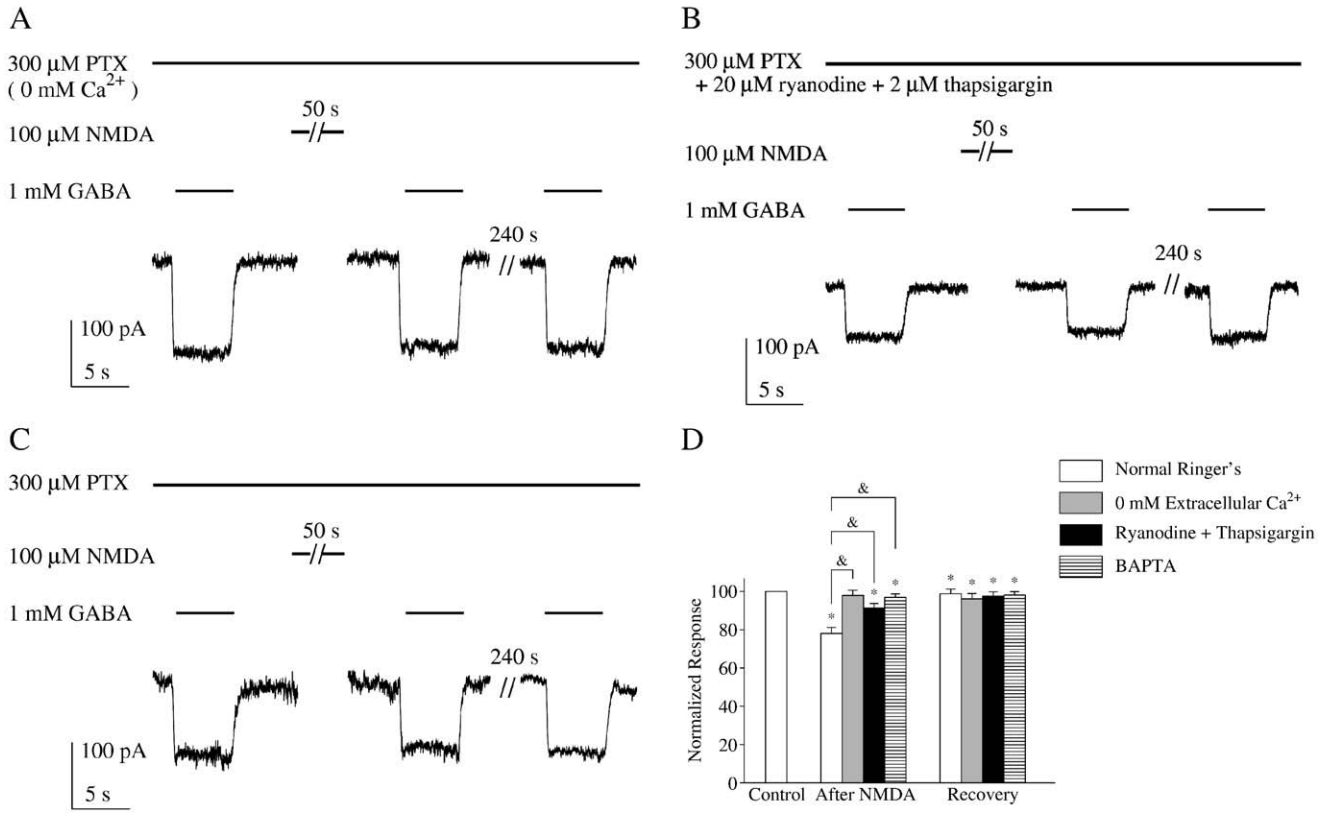

Fig. 4 – (A) An example of the GABA transporter currents recorded in Ca^{2+} free Ringer's solution. (B) The GABA transporter currents measured in an H1 cell in which the Ca^{2+} release/uptake of the intracellular Ca^{2+} stores was blocked by ryanodine + thapsigargin. (C) The GABA transporter currents measured when 10 mM BAPTA was added in the Ca^{2+}-free intracellular solution. (D) The statistics for the GABA transporter currents (normalized against control, mean ± SD, $n=5$ for each) measured during control, after NMDA pre-application and recovery (white columns: normal Ringer's solution; grey columns: Ca^{2+}-free Ringer's solution; black columns: ryanodine + thapsigargin; striped columns: 10 mM BAPTA in the Ca^{2+}-free intracellular solution). $^{*}p<0.05$ (paired t-test, as compared to control). $^{\&}p<0.05$ (unpaired t-test, as compared to normal Ringer's).

recovery level was 98.13 ± 1.82% (mean ± SD) of the control level ($p<0.05$, paired t-test).

These results suggest that the Ca^{2+} influx through NMDA receptors is important for the modulation of the GABA transporter current, and the Ca^{2+} released by the intracellular Ca^{2+} store is involved in the process.

3. Discussion

GABA transporters expressed on the H1 horizontal cells of carp retina are of GAT-1 subtype, which can be inhibited by GAT-1 inhibitor SKF-89976-A (Takahashi et al., 1995). These GABA transporters are responsible for GABA uptake and release (Richerson and Wu, 2003; Schwartz, 2002). Under physiological conditions, GABA uptake occurs during illumination when the horizontal cells are hyperpolarized, and GABA is released during darkness when the horizontal cells are depolarized (Schwartz, 2002). In the present study, the horizontal cells were voltage-clamped at −60 mV and were in a state of hyperpolarization. Under such experimental condition, the GABA transporter function should be related to GABA uptake which produces an inward GABA transporter current. Such GABA-induced current persists in the presence of PTX but can be abolished by the GABA transporter blocker.

The experimental results of the present study demonstrate that the application of exogenous NMDA can down-regulate the GABA transporter-mediated current in freshly isolated H1 cells of carp retina. The NMDA modulatory effect depends upon the presence of Ca^{2+}, since the inhibitory effect was significantly attenuated when the extracellular Ca^{2+} was removed, or Ca^{2+} release/uptake of the intracellular Ca^{2+} store was blocked. The suppression effect could also be eliminated when the intracellular Ca^{2+} changes of the cells were attenuated by 10 mM BAPTA in intracellular solution.

The recovery levels of GABA transporter currents in the present study were all close to the control levels (>95%), but not complete. One of the possible reasons is that there is some time-dependent rundown of the GABA transporter current. To check if this is the case, the GABA transporter currents were recorded following the time course the same as that during drug application. Without any drug application, the GABA transporter currents were decreased to 97.80 ± 1.51% (mean ± SD, $n=5$) of the control after 5 min (data not shown). This confirms that the GABA transport currents had a small amount of rundown over time in our experimental conditions.

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While calcium is important for the vesicle fusion and transmitter release in vesicular release, the transporter-mediated GABA release was suggested to be Na^+-dependent but Ca^{2+}-independent (Yazulla and Kleinschmidt, 1983; Yazulla, 1985). It was also reported that when the extracellular Ca^{2+} was replaced with Co^{2+}, the release of GABA was unaffected (Schwartz, 1982). Although the release of GABA does not require Ca^{2+}, Kreitzer et al (2003) reported that glutamate regulates GABA uptake in the horizontal cell of skate retina through a Ca^{2+}-dependent process. Ca^{2+}-influx via AMPA receptors down-regulates the GABA uptake of the transporters. This AMPA receptor-mediated down-regulation of GABA transporter function was observed in our experiments (unpublished observations). It was also observed in our experiments that membrane depolarization induced a decrease in GABA transporter current, which might be due to activation of voltage-gated channels (unpublished observations). On the other hand, application of thapsigargin could also inhibit the GABA uptake of the transporters, which is related to an increased intracellular Ca^{2+} by the Ca^{2+} leak of intracellular stores while the Ca^{2+} uptake was blocked at the same time (Kreitzer et al., 2003).

Ca^{2+} influx can occur through glutamate receptors and voltage-gated Ca^{2+} channels in the retinal horizontal cells (Schubert et al., 2006). Much previous research indicated that glutamate receptors expressed in retinal horizontal cells are of AMPA subtype, with the only exception being catfish horizontal cells, which express NMDA receptors. Our previous work also showed that Ca^{2+}-permeable AMPA receptors were expressed in carp H1 cells (Huang and Liang, 2005). However, it was recently found that functional NMDA receptors are expressed in carp H1 type horizontal cells (Shen et al., 2006). The functions of NMDA receptors in the outer retina are not clear. In the present study, it is found that the activation of NMDA receptors can down-regulate the GABA transporter-mediated current. Under our experimental condition, the voltage-gated Ca^{2+} channels were not activated because the horizontal cells were voltage-clamped at −60 mV. Moreover, the application of NMDA selectively activates NMDA subtype glutamate receptors. Therefore extracellular Ca^{2+} can enter the H1 cell only through NMDA receptors in these conditions. When the extracellular Ca^{2+} was removed, the NMDA modulatory effect was eliminated, suggesting that Ca^{2+} influx through the NMDA receptors is required for the modulation.

The role of Ca^{2+} release from the intracellular Ca^{2+} store was also investigated. Activation of Ca^{2+}-permeable AMPA receptors in the horizontal cell can cause an increase of intracellular Ca^{2+} concentration and subsequent Ca^{2+}-induced-Ca^{2+}-release (CICR) from intracellular Ca^{2+} stores. We also found that activation of NMDA receptors caused similar intracellular Ca^{2+} changes in the carp retinal horizontal cell (Wang et al., 2008). The NMDA-initiated suppression of GABA transporter current was significantly reduced when the Ca^{2+} release/uptake of intracellular Ca^{2+} store had been block by application of ryanodine + thapsigargin. When the change of intracellular Ca^{2+} was reduced by BAPTA, NMDA-initiated suppression of GABA transporter current was also decreased. This implies that the Ca^{2+} release from the intracellular Ca^{2+} store is involved in the modulation.

In the present study, the horizontal cells were voltage-clamped at −60 mV, application of NMDA can down-regulate the GABA transporter-mediated current through Ca^{2+} processes in Mg^{2+}-free Ringer's solution. Under physiological conditions, the NMDA receptors are not activated during hyperpolarization because of the voltage-dependent Mg^{2+} blockade. However, in the dark, the retinal horizontal cells are depolarized to a level around −20 mV. At such membrane potential, GABA is released via GABA transporters (Schwartz, 2002). On the other hand, both NMDA receptors and AMPA receptors are activated by glutamate that is released by photoreceptors. Ca^{2+} can enter the cell through either NMDA receptors or Ca^{2+} permeable AMPA receptors. It was reported that in the horizontal cell of skate retina, glutamate suppression effect is mediated by AMPA receptors (Kreitzer et al., 2003), while in the horizontal cell of carp retina, such glutamate suppression effect is mediated by both of Ca^{2+} permeable AMPA receptors and NMDA receptors. The modulation of GABA transporters initiated by activation of both NMDA receptors and AMPA receptors by glutamate was observed in the carp retina (unpublished observation). In the modulation, AMPA receptors and NMDA receptors share the same intracellular calcium pathway. Since AMPA receptors display very rapid and significant desensitization, and NMDA receptors do not desensitize as quickly or as fully, NMDA receptors might play a significant role in the regulation of GABA transporter activities under physiological conditions.

4. Experimental procedures

4.1. *Cell isolation*

Horizontal cells were enzymatically dissociated from retinas of adult carp (*Carassius auratus*, 15–20 cm body length), as described previously (Huang and Liang, 2005). Briefly, retinas were isolated from carp, and incubated for 20 min at room temperature in 4 ml Hank's solution with 25 U/ml papain and 4 mg L-cysteine. The retinas were rinsed and stored in the Hank's solution at 4 °C. Cells were freshly dissociated from the retinal pieces by gentle trituration in Ringer's solution and the cell suspension was placed onto a plastic dish. H1 horizontal cells were identified by their characteristic morphology.

4.2. *Whole-cell recording and drug application*

Whole-cell recordings, voltage-clamped at −60 mV, were obtained using 5–8 M Ω patch pipette pulled from borosilicate glass (Sutter Instrument Inc., USA) using a horizontal puller (P87, Sutter Instrument Inc., USA). The pipette was filled with intracellular solution, mounted on a motor-driven micromanipulator (MC1000e, SD Instrument Inc., USA), and was connected to a patch amplifier (Axopatch 200B, Axon Instrument Inc., USA). An agar/NaCl bridge connected to the recording chamber with an Ag/AgCl wire inside was used as a reference electrode. Fast capacitance, cell capacitance transients, and 70% of the series resistance of the recording electrode were compensated. Data acquisition was performed using AxoScope software (Axon Instrument Inc., USA), with sample rate being 1 kHz and was lowpass filtered (0 ~ 1 kHz). The recorded data were analyzed by Clampfit 9.2 software (Axon Instrument Inc., USA).

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For brief application of GABA and NMDA, the superfusion system (DAD-12, ALA Scientific Instruments, USA) was used. Other chemicals were bath-applied with the perfusate at a flow rate of 1 ml/min. In all experiments, NMDA was always co-applied with 100 μM glycine, which alone could not induce a detectable current.

4.3. *Solutions*

Hank's solution contained (in mM) 120.0 NaCl, 3.0 KCl, 0.5 $CaCl_2$, 1.0 $MgSO_4$, 1.0 Na-pyruvate, 1.0 NaH_2PO_4, 0.5 $NaHCO_3$, 20.0 HEPES and 16.0 glucose. Mg^{2+}-free Ringer's solution contained (in mM) 120.0 NaCl, 5.0 KCl, 2.0 $CaCl_2$, 10.0 HEPES and 16.0 glucose. Ryanodine and thapsigargin were prepared in dimethyl sulfoxide (DMSO) and diluted to the required final concentration in Ringer's solution (with the final concentration of DMSO <0.5%). Picrotoxin (PTX), NMDA, DL-2-amino-5-phosphonopentanoic acid (AP-5) and GABA were dissolved in Ringer's solution. The pH value for the perfusate was adjusted to 7.4 with NaOH. The intracellular solution for patch electrode contained (in mM) 140.0 CsCl, 0.05 $CaCl_2$, 1.0 $MgSO_4$, 0.5 EGTA, 10.0 HEPES. The pH value was adjusted to 7.3 with CsOH. All the drugs were purchased from Sigma (St. Louis, MO, USA).

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