Dynamic Metabotropic Control of Intrinsic Firing in Cerebellar Unipolar Brush Cells

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Russo MJ, Yau H-J, Nunzi M-G, Mugnaini E, Martina M. Dynamic metabotropic control of intrinsic firing in cerebellar unipolar brush cells. J Neurophysiol 100: 3351–3360, 2008. First published October 22, 2008; doi:10.1152/jn.90533.2008. Neuronal firing is regulated by the complex interaction of multiple depolarizing and hyperpolarizing currents; intrinsic firing, which defines the neuronal ability to generate action potentials in the absence of synaptic excitation, is particularly sensitive to modulation by currents that are active below the action potential threshold. Cerebellar unipolar brush cells (UBCs) are excitatory granule layer interneurons that are capable of intrinsic firing, which is mediated by voltage-gated sodium channels and a transient receptor potential (TRP)–like conductance (Russo et al. 2007). The UBC typically has a single, short dendrite terminating in a brush of dendrioles; it receives glutamatergic input on the brush from an individual mossy fiber (Diño et al. 2000) through an unusually extensive synapse with multiple presynaptic sites, which results in fast and peculiarly slow currents mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors (Mugnaini et al. 1994; Rossi et al. 1995). Moreover, cerebellar UBCs express one or more types of metabotropic glutamate receptors (mGluRs) (Neki et al. 1996a,b; Nunzi et al. 2002; Ohishi et al. 1993, 1998; Sekerkova et al. 2004; Takács et al. 1999) that are highly enriched in the peri- and extrasynaptic portion of the membrane of the brush dendrioles and are also present in the plasma membrane of the dendritic trunk and cell body (Jaarsma et al. 1998). Here we show that activation of group II mGluRs produces dynamic control of the intrinsic firing of UBCs.

METHODS

Slice preparation

All experiments conformed to protocols approved by the Northwestern University Animal Care and Use Committee. We followed guidelines issued by the National Institutes of Health and the Society for Neuroscience to minimize the number of animals used and their suffering.

CD1 male, 24- to 38-day-old mice (Charles River Laboratories, Wilmington, MA; or Harlan, Indianapolis, IN) were deeply anesthetized with isoflurane (0.3 ml in 1 L administered for ~90 s) and killed by decapitation. The cerebella were quickly removed from the skull and placed in ice-cold modified artificial cerebrospinal fluid containing (in mM): 87 NaCl, 25 NaHCO3, 2.5 KCl, 1.25 NaH2PO4, 0.5 CaCl2, 7 MgCl2, 75 sucrose, 25 glucose, and 1 kynurenic acid, bubbled with 95% O2-5% CO2. Parasagittal slices (300 μm thick)...

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were cut from the vermis using a vibrating blade microtome (Ted Pella, Redding, CA). Slices were incubated at 35°C for 20–30 min and then stored at room temperature. All recordings were performed from cells in lobules IX and X. During recording, slices were continuously superfused with physiological extracellular solution containing (in mM): 125 NaCl, 25 NaHCO₃, 2.5 KCl, 1.25 NaH₂PO₄, 1.5 CaCl₂, and 25 MgCl₂, and 25 glucose, bubbled with 95% O₂-5% CO₂. Slices were visualized with an Axioskop FS (Zeiss, Jena, Germany) upright microscope using infrared differential interference contrast videomicroscopy under a water-immersion ×60 objective.

**Electrophysiological recordings**

Pipettes were pulled from Garner glass (Claremont, CA) using a horizontal puller (P97, Sutter Instruments, Novato, CA) and filled with internal solution consisting of (in mM): 140 K-gluconate, 2 MgCl₂, 10 EGTA, 2 Na₂ATP, 0.1 NaGTP, and 10 HEPES (pH 7.3 with KOH). Pipette tip resistances in working solutions ranged from 5 to 8 MΩ yielding series resistances of 10 to 25 MΩ.

Recordings were performed at 22–24°C (except for the data in Fig. 10) using an Axopatch 200B amplifier (Axon Instruments, Foster City, CA; now MDS Analytical Technology, Toronto, Canada). Current signals were low-pass filtered at 2 or 5 kHz (four-pole low-pass Bessel filter on amplifier) and digitized (10 kHz) using a Digidata 1321A controlled by pClamp8 software interface (MDS Analytical Technology). Signals from current-clamp recordings were sampled at 20 kHz and filtered at 10 kHz.

**Immunocytochemistry**

Two CD1 mice, 35 days old, were deeply anesthetized with sodium pentobarbital (administered intraperitoneally; 60 mg/kg body weight) and perfused through the ascending aorta with saline followed by 4% freshly depolymerized paraformaldehyde in 0.1 M PB (pH 7.4). After perfusion, brains were maintained in situ at room temperature for 1 h, dissected, and then cryoprotected in 30% sucrose dissolved in phosphate-buffered saline (PBS) at 4°C. Serial sections of the vermis (20 μm thick) were cut in the sagittal plane on a freezing stage microtome and collected in PBS. Sections for double-label immunofluorescence were blocked with 3% normal goat serum/1% bovine serum albumin/0.2% Triton X-100 in Tris-buffered saline followed by incubation at 4°C for 24–48 h with pairs of the following primary antibodies: rabbit polyclonal anti-calretinin (1:1,000; cat #AB5054, Chemicon, now Millipore, Billerica, MA) and mouse anti-mGluR2 (1:1000; produced, characterized, and given to us by Dr. R. Shigemoto, Myodaiji, Okazaki, Japan); or rabbit polyclonal anti-mGluR1α (1:1,000; gift of Dr. R. Shigemoto) and mouse anti-mGluR2 (as above). After rinsing, primary antibodies were visualized by the appropriate secondary antibodies coupled to Alexa 488 or Alexa 568 (Molecular Probes/Invitrogen, Carlsbad, CA). Sections were coverslipped with Vectashield (Vector Laboratories). Each primary antibody recognized a single band in immunoblots. For all experiments, control sections incubated without the appropriate primary antibody lacked immunoreaction signal.

Immunofluorescence images of brain stem sections were acquired with a Spot RT CCD video camera (Diagnostic Instruments, Sterling Heights, MI) mounted on a Nikon Eclipse E800 microscope. Laser scanning confocal images were obtained with a Nikon PCM 2000 confocal microscope system (Melville, NY), mounted on the Eclipse microscope. Images were analyzed individually or in z-stacks of different depths. For colocalization experiments type DF immersion oil (Fryer, Huntley, IL) was used with either a ×40 plan-fluor lens (numerical aperture [NA] 1.3) or a ×60 plan-apochromatic lens (NA 1.4). To minimize spillover between the channels the images were sequentially acquired and saved as tiff files with 300 pixels/in. resolution. All images were processed with Adobe Photoshop to adjust brightness/contrast without further editing.

**RESULTS**

**mGluR activation inhibits intrinsic firing**

We performed whole cell recordings from UBCs in acute cerebellar slices from 24- to 38-day-old mice, an age at which these neurons are believed to have attained full maturation (Morin et al. 2001). A first set of experiments was designed to test the presence of background currents modulated by mGluRs. To this aim, the broad-spectrum mGluR agonist (±)-trans-ACPD (0.1 mM, hereafter t-ACPD) was applied to the bathing solution during current-clamp recordings obtained in the presence of blockers of fast synaptic transmission (3 mM kynurenic acid, 0.1 mM picrotoxin, and 1 μM strychnine).
t-ACPD induced a membrane hyperpolarization that strongly inhibited intrinsic firing (Fig. 1) and, in some cases, the magnitude of the hyperpolarization was large enough that it led to a complete cessation of firing; this effect was promptly reversible on washout of t-ACPD (Fig. 1A). To understand the mechanism mediating the hyperpolarization we first examined the effect of t-ACPD on the input resistance of UBCs. Bath application of t-ACPD consistently led to a decrease in input resistance (from $15.2 \pm 2.2$ to $11.1 \pm 1.7 \text{ k}\Omega\cdot\text{cm}^2$, $P < 0.05$, 9 cells, Fig. 1D), suggesting the opening of a background conductance. Moreover, the magnitude of the input resistance drop showed a linear correlation with the effect of t-ACPD on firing frequency ($r = 0.71$, $P < 0.05$, Fig. 1E), which suggested that the t-ACPD-induced hyperpolarization was the main reason for the reduction in firing frequency. These data showed that mGluR activation in UBCs leads to inhibition of intrinsic firing through the modulation of a background conductance.

To further characterize the properties of the mGluR-dependent current, voltage-clamp recordings were obtained in control conditions and in the presence of t-ACPD (100 µM). Cells were patched in whole cell and the voltage was slowly ramped from $-112$ to $-62$ mV (Fig. 2, A and B). As we expected, t-ACPD increased the background current. The mGluR-sensitive current, obtained by digital subtraction (Fig. 2C), had a reversal potential of $-88 \pm 7$ mV ($n = 3$) and showed inwardly rectifying current–voltage ($I–V$) relation suggesting that the mGluR are coupled to KCNJ channels.

**Basal activation of mGluR receptors in UBCs**

Acutely dissociated cerebellar UBCs have been shown to express a G-protein–coupled inward rectifier current that is strongly sensitive to barium (Knoflach and Kemp 1998). Thus we tested whether barium (500 µM) could antagonize the effect of t-ACPD on the current. Cells were first exposed to a saturating concentration of t-ACPD to fully activate the current and then barium was added to the bath solution. Barium not only completely abolished the current that was previously activated by t-ACPD, but also induced a further decrease of the background potassium current, indicating a basal level of mGluR activation in the slice (Fig. 2B). The $I–V$ relation of the barium-sensitive current was very similar to the t-ACPD activated current (Fig. 2D), suggesting that both currents were mediated by the same channels. Having shown that barium effectively blocks the t-ACPD-sensitive current, we reasoned that, if activation of the background potassium current is the only mechanism responsible for the inhibition of intrinsic firing by t-ACPD, barium should rescue intrinsic firing in cells...
an increase was paralleled by an increase of the input resistance when barium was applied on top of t-ACPD (Fig. 3); this activation, the firing frequency of UBCs actually increased ally, in keeping with the idea of a basal level of mGluR activation. Figure 3 shows that this was the case: barium (0.5 mM) rescued intrinsic firing. Addition-
inhibited by mGluR activation. Figure 3 shows that this was the case: barium (0.5 mM) rescued intrinsic firing. Additionally, in keeping with the idea of a basal level of mGluR activation, the firing frequency of UBCs actually increased when barium was applied on top of t-ACPD (Fig. 3); this increase was paralleled by an increase of the input resistance (from 16.9 ± 3 kΩ·cm² in control conditions to 26.8 ± 3.5 kΩ·cm² in t-ACPD + barium, Fig. 3F, n = 5, P < 0.05), as expected, if barium blocks a background conductance.

Identification of the mGluR subtype regulating intrinsic firing in UBCs

Currents linked to group II mGluRs have been described in dissociated UBCs (Knollflach and Kemp 1998); therefore we investigated whether activation of group II mGluRs by the selective agonist (2R,4R)APDC (10 μM) affects intrinsic firing of UBCs in acute slices. Indeed, group II mGluR activation reduced the firing frequency through membrane hyperpolarization (Fig. 4), similarly to the effect described for the broad-spectrum mGluR agonist t-ACPD. Further confirmation of the identity of the mGluR mediating the inhibitory response in UBCs was obtained from a set of experiments in which the (2R,4R)APDC-activated current was reversed by the selective group II mGluR antagonist LY341495. In the nine cells tested for these experiments, (2R,4R)APDC reduced the average firing frequency from 22 ± 1.7 Hz in control to 13.7 ± 2.9 Hz (n = 9, P < 0.05); addition of LY341495 on top of (2R,4R)APDC almost completely reversed the effect of (2R,4R)APDC (the firing frequency increased from 13.7 ± 2.9 Hz to 18.4 ± 2.6 Hz, n = 9, P < 0.05, Fig. 5). Similar results were obtained for the input resistance: (2R,4R)APDC-mediated mGluR activation reduced the input resistance from 17.5 ± 3 to 11.3 ± 1.5 kΩ·cm² (n = 8, P < 0.05); application of LY341495 on top of (2R,4R)APDC completely reversed the effect of (2R,4R)APDC and the input resistance value rebounded to 21.3 ± 2.7 kΩ·cm² (n = 8, P < 0.05, Fig. 5C). It is noteworthy that in six of eight cells tested the input resistance value measured in (2R,4R)APDC + LY341495 was actually larger than that in the control condition [before application of (2R,4R)APDC], supporting the idea that the barium-sensitive background current described in Fig. 3 is regulated by type II mGluR.

In separate experiments, the effect of the specific group I mGluR agonist t-quissquale (5 μM) on UBCs was also tested (Supplemental Fig. S1).1 t-Quissqualate did not produce any notable effect on either the firing frequency (15 ± 2.1 vs. 15.7 ± 2.4 Hz in control and t-quinqueulate, respectively), n = 4) or the input resistance (11.5 ± 1.9 vs. 12.5 ± 1.4 kΩ·cm² in control and t-quinqueulate, respectively, n = 4), thus suggesting that group I mGluRs do not play an important role in controlling UBC firing.

Group II mGluRs are widely expressed by UBCs

Cerebellar UBCs consist of two morphologically similar but chemically diverse subsets, one of which is characterized by expression of the calcium binding protein calretinin (CR) and the other by expression of the metabotropic glutamate receptor mGluR1α (Nunzi et al. 2002). Although previous immunocytochemical investigations identified the presence of mGluR2 expressing UBCs in the rodent cerebellum, these studies did not further investigate the chemical phenotypes of the mGluR2-positive cells. Therefore we tested whether expression of mGluR2s is a property shared by the entire UBC population or whether it is restricted to one or the other of the two subsets. As shown in Fig. 6, the mGluR2 signal colocalized with both CR and mGluR1α in mouse (as well as rat, not shown) UBCs. Thus the effect of activation of group II mGluRs on cell firing may be considered a general property of UBCs, as was also suggested by the homogeneity of the electrophysiological responses.

Properties of the mGluR-activated potassium current

As shown in Fig. 2, the mGluR-activated potassium current of UBCs is sensitive to barium, the most widely used blocker of background potassium currents. Blockade by barium, however, does not offer useful hints about the molecular composition of the channels because this is a property shared by all members of the KCNK and KCNJ families. Tertiapin is a bee venom peptide that effectively blocks selected members of the KCNJ family (Jin and Lu 1998; Ramu et al. 2004). Interestingly, and somewhat unexpectedly, tertiapin (300 nM) produced no detectable effect on the intrinsic firing of UBCs (from

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1 The online version of this article contains supplemental data.
8.5 ± 2 Hz in control to 8.0 ± 1.4 Hz in the presence of tertiapin, \( n = 7 \), Fig. 7) and only a modest (nonsignificant) increase in the input resistance (19.5 ± 1.8 kΩ·cm² in control and 24.3 ± 3.4 kΩ·cm² in tertiapin, \( P > 0.05, n = 7 \), not shown). This result suggests that Kir3.3 or 3.4 subunits, which are highly tertiapin sensitive, do not provide a major contribution to the background potassium current in UBCs in basal slice conditions. Although these data showed that there is no significant activation of tertiapin-sensitive currents by the basal glutamate levels present in acute slices, it was still possible that the currents mediated by t-ACPD-induced mGluR activation are tertiapin sensitive. Figure 8 shows that this was the case: when applied following mGluR activation by 100 μM t-ACPD, tertiapin caused a significant cell depolarization (from −96.9 ± 7 to −89.5 ± 5.6 mV, \( P < 0.05 \), seven cells, Fig. 8, A and B) in parallel with an increase of the input resistance (from 9.4 ± 1.9 kΩ·cm² in t-ACPD to 13.4 ± 2.5 kΩ·cm² in t-ACPD + tertiapin, \( n = 4 \), \( P < 0.05 \), Fig. 8D), although it never restored intrinsic firing. Thus the background potassium current of UBCs consists of two distinct components, which can be distinguished on the basis of their sensitivity to tertiapin. Of these components, the tertiapin-insensitive one appears to have the greater impact on intrinsic firing, although the tertiapin-sensitive component significantly adds to the hyperpolarization and the regulation of the input resistance. This predominance of the tertiapin-insensitive current is also reflected in the \( J-V \) plots of the barium-sensitive current recorded in control conditions and the LY341495-sensitive current recorded after mGluR activation with (2R,4R)APDC (Fig. 9). The two \( J-V \) curves look similar and, in contrast to inward rectifier currents mediated by channels containing tertiapin-sensitive subunits (e.g., Kir3.1/3.4; Dibb et al. 2003), both show some degree of saturation at very negative membrane potentials.

**mGluR activation inhibits firing of UBCs at near-physiological temperature**

All the experiments described so far were performed at 22–24°C. However, basal slice levels of glutamate might vary with temperature; if so, the effect of mGluR activation on
intrinsic firing may differ at near-physiological temperature. Therefore we tested the effect of t-ACPD on intrinsic firing of UBCs at about 35°C. Figure 10 shows that, similar to what was observed at room temperature, UBCs are intrinsically firing at about 35°C and mGluR activation has a strong and reversible inhibitory effect. In response to t-ACPD application, the firing frequency dropped from 11.4 ± 2.9 Hz in control to 0.54 ± 0.59 Hz in t-ACPD (n = 6, P < 0.05). Similar to the effect observed at lower temperature, the decrease in firing frequency was due to a large hyperpolarization (Fig. 10A).

**DISCUSSION**

We performed patch-clamp recordings from acute mouse cerebellar slices to investigate the regulation of intrinsic firing in UBCs. We found that mGluRs show a basal level of activation and that the up- or down-regulation of inward rectifier currents, most likely linked to group II mGluRs, effectively modulate the intrinsic firing of UBCs. Because we show that mGluR2 protein is present in both CR+/mGluR1− and CR−/mGluR1α+ UBCs, the effects described here are most likely a general property of the entire UBC population.

**Postsynaptic action of group II mGluR**

Inhibitory effects of group II mGluRs are quite common in the CNS. In most cases, however, mGluR2 action is mostly presynaptic (Han et al. 2006; Hayashi et al. 1993; Manzoni et al. 1995). Postsynaptic effects of group II mGluRs are less frequent, although they have been previously described; in the

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**FIG. 5.** Group II mGluR antagonist LY341495 [(2S)-2-amino-2-[(1S,2S)-2-carboxyxylylprop-1-yl]-3-(xanth-9-yl) propanoic acid] reverses the effects of (2R,4R)APDC. A: current-clamp recording from a UBC; the breaks in the axis represent times in which the continuous current-clamp recording was interrupted to perform voltage-clamp measurements. In this cell mGluR activation by (2R,4R)APDC (10 μM) completely abolished intrinsic firing; addition of the group II mGluR antagonist LY341495 (2 μM) on top of (2R,4R)APDC reversed the effect and re-established intrinsic firing. B and C: bar charts summarizing the change of input resistance and firing frequency induced by (2R,4R)APDC and LY341495 on top of (2R,4R)APDC in 6 UBCs. Note that, on average, the value of input resistance in the presence of LY341495 reached values slightly higher than in control conditions, suggesting a basal type II mGluR activity in the slice.

**FIG. 6.** Group II mGluR expression is abundant in both UBC subtypes. Immunohistochemical staining of mouse cerebellar slices shows that both mGluR1α-positive and calretinin-positive UBCs abundantly express mGluR2. A: immunostaining obtained with mGluR2-specific antibody shows intense staining of the UBC brush (Br) and faint staining of the somatic (s) plasma membrane. B: the corresponding portions of the same cell were immunopositive for GluR1α. C: merged image of A and B. D–F: example of mGluR2 staining in a calretinin-positive UBC; note that calretinin immunostain is present throughout the cytoplasm, thus obfuscating the cell nucleus. Scale bar: 10 μm.
cerebellum, they were demonstrated in Golgi cells (Watanabe and Nakanishi 2003), which are another type of intrinsically firing granular layer interneuron. In UBCs, mGluR activation has large postsynaptic effects through the activation of inward rectifier channels. These data are consistent with the detection in UBCs of mGluR2 message and protein expression (Jaarsma et al. 1998; Neki et al. 1996a,b; Ohishi et al. 1993, 1998; Sekerkova et al. 2004) and of mGluR2-dependent inward rectifier current in acutely dissociated rat UBCs (Knoflach and Kemp 1998).

Nature of the background potassium current

It has been suggested that G-protein–activated inwardly rectifying potassium channel 2 (GIRK2) subunits mediate postsynaptic currents activated by several metabotropic receptors (Lüscher et al. 1997). A current with functional properties resembling those of GIRK channels has been described in dissociated UBCs (Knoflach and Kemp 1998). More recently, Harashima et al. (2006) and Aguado et al. (2008) have shown that mouse UBCs express the GIRK2 and GIRK3 subunits. These data raise the possibility that the currents activated in UBCs by ambient glutamate levels may be mediated by GIRK channels. Analysis of the tertiapin sensitivity, on the other hand, shows that at least two components, one sensitive and one insensitive to this toxin, contribute to the background potassium current in UBCs. Because tertiapin sensitivity is a dominant feature in heteromeric channels composed of both tertiapin-sensitive (such as Kir3.3 and 3.4) and -insensitive (such as Kir3.1) subunits (Ramu et al. 2004), the fact that tertiapin did not affect intrinsic firing frequency seems to exclude a major contribution of GIRK3 (Kir3.3) subunits to the tonic potassium current in acute slices. At the same time, pharmacological mGluR activation produced a current that was partly sensitive to tertiapin. A parsimonious interpretation of the data suggests that the same mix of currents is active in basal condition and after pharmacological mGluR activation and that the larger currents in t-ACPD allow better resolution of the toxin effect. The possibility of a pure GIRK2-mediated current, on the other hand, is also unlikely because the $I-V$ plot of the LY341495-sensitive current (Fig. 9) shows saturation at membrane potentials negative to $-130$ mV; although this is similar...
to the background potassium current described in acutely dissociated UBCs (Knoflach and Kemp 1998), it differs from the typical features of the GIRK2-mediated current expressed in heterologous expression systems (Inanobe et al. 1999). Thus unambiguous identification of the molecular composition of the mGluR-sensitive potassium channel(s) in UBCs will require further experiments.

Complex action of glutamate on UBCs

The findings presented here suggest a complex and somewhat unexpected action of glutamate on cerebellar UBCs. It is known that the effect of synaptically released glutamate on UBCs results in unusually long-lasting AMPA and NMDA responses due to the anatomical structure of the glomerulus (Nunzi et al. 2001; Rossi et al. 1995). Our results show that glutamate can have inhibitory effects as well. Activation of mGluRs by spillover of glutamate, which is likely to follow synaptic release because of the peculiar structure of the mossy fiber–UBC synapse in which mGluRs are characteristically localized lateral to the postsynaptic density (Jaarsma et al. 1998), leads to the activation of an inwardly rectifying, barium-sensitive potassium conductance. The ensuing hyperpolarization strongly inhibits intrinsic excitability, possibly leading to a complete elimination of intrinsic firing.

Functional considerations

It has been proposed that in vivo neurons may switch between pace-making and silent mode in relation to behavioral requirements (Ramirez et al. 2004). Thus the neuromodulation described here may have a major impact. Because of their

FIG. 9. The barium-(Ba-) and LY341495-sensitive currents have similar properties. A: current traces of the Ba-sensitive component. Voltage-clamp recordings were obtained in response to a set of voltage pulses from −152 to −72 mV (from a holding of −90 mV) in control conditions and in the presence of 0.5 mM Ba. The traces shown in the figure represent the Ba-sensitive component obtained by off-line digital subtraction. B: current–voltage (I–V) plot of the Ba-sensitive current. C: same voltage protocol as in A; LY341495 was bath applied to the slices after mGluR activation by (2R,4R)APDC (0.01 mM). The traces shown represent the LY341495-sensitive component (obtained by digital subtraction). D: I–V plot of the LY341495-sensitive current. Note that both currents show some saturation at potential negative to −130 mV.

FIG. 10. mGluR regulation of UBCs’ firing frequency is maintained at near physiological temperature. A: current-clamp recording obtained from a UBC at about 35°C and without injection of any bias current; similar to what was observed at room temperature, bath application of t-ACPD (100 μM) reversibly hyperpolarized the cells, often leading to a complete stop of intrinsic firing. B: bar chart summarizing the average UBC’s firing frequency at about 35°C in control condition and after mGluR activation by t-ACPD (6 cells, P < 0.05).
mGluRs REGULATE UBC FIRING


REGULATING NEURONAL ACTIVITY

mGluRs REGULATE UBC FIRING


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