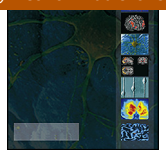
Neuroscience Letters 559 (2014) 13–17

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Hippocampal ether-à-go-go1 potassium channels blockade: Effects in the startle reflex and prepulse inhibition

A.C. Issy[a,1], J.R. Fonseca[b,1], L.A. Pardo[c], W. Stühmer[c], E.A. Del Bel[a,*]

[a] Department of Morphology Physiology and Basic Pathology, University of São Paulo (USP), Dental School of Ribeirão Preto, Brazil
[b] Federal University of São Paulo (UNIFESP), Brazil
[c] Department of Molecular Biology of Neuronal Signals, Max-Planck Institute of Experimental Medicine, Gottingen, Germany

HIGHLIGHTS

- Eag1 K^+ channels blockade in the dentate gyrus of the hippocampus did not modify apomorphine-disruptive effects in the PPI.
- Dentate gyrus surgery inducing decreased startle response was restored by the Eag1 antibody.
- The role of Eag1 K^+ channels in the startle response merits further investigation.

ARTICLE INFO

Article history:
Received 6 August 2013
Received in revised form
13 November 2013
Accepted 16 November 2013

Keywords:
Dopamine
Prepulse inhibition
Schizophrenia
Eag1
Kv10.1
Startle reflex

ABSTRACT

Recently, our group described the *ether-à-go-go1*(Eag1) voltage-gated potassium (K^+) channel (Kv10.1) expression in the dopaminergic cells indicating that these channels are part of the diversified group of ion channels related to dopaminergic neurons function. The increase of dopamine neurotransmission induces a reduction in the prepulse inhibition (PPI) of the acoustic startle reflex in rodents, which is a reliable index of sensorimotor gating deficits. The PPI response has been reported to be abnormally reduced in schizophrenia patients. The role of Eag1 K^+ channels in the PPI reaction had not been revealed until now, albeit the singular distribution of Eag1 in the dentate gyrus of the hippocampus and the hippocampal regulation of the startle reflex and PPI. The aim of this work was to investigate if Eag1 blockade on hippocampus modifies the PPI-disruptive effects of apomorphine in *Wistar* rats. Bilateral injection of anti-Eag1 single-chain antibody into the dentate gyrus of hippocampus did not modify apomorphine-disruptive effects in the PPI response. However, Eag1 antibody completely restored the startle amplitude decrease revealed after dentate gyrus surgery. These potentially biological important phenomenon merits further investigation regarding the role of Eag1 K^+ channels, mainly, on startle reflex modulation, since the physiological role of these channels remain obscure.

1. Introduction

Ether-à-go-go-related gene (ERG) potassium (K^+) channel is mainly expressed in the human and rodents adult brain [23,24]. ERG K^+ channels belong to a superfamily of voltage-activated K^+ channels encoded by three distinct gene subfamilies, including *ether-à-go-go* (*eag*), *ether-à-go-go*-like (*elk*), and *ether-à-go-go*-related (*erg*) genes [8,42]. Among them, the Eag K^+ channel appears to be the only mainly neuron-specific and localized to synapses [18]. Eag K^+ channel is represented by the Eag1 gene (KCNH1, K_v10.1) [26,42] and Eag2 (KCNH5, K_v10.2) [19,23]. Highest Eag1 gene expression is found in the cerebral cortex, hippocampus, cerebellum and hypothalamus of human and rat, which greatly overlaps with *Eag*1 protein expression [24]. However, the function of Eag1 K^+ channels in the central nervous system is still unknown [26,27]. It was suggested that the lateral diffusion of Eag1 ion channels acts as a dynamical mechanism to accrue these channels to the synaptic terminals, where they should play a pivotal role for synaptic function and plasticity [11]. The expression of the Eag1 K^+ channel is high in the nigrostriatal pathway and it is co-localized with the dopaminergic cells [7]. This data suggests that these channels may well participate in the physiology of the dopaminergic system [7].

Sensorimotor gating is the ability to gate out irrelevant stimuli, a normal central inhibitory processes expression, and its ability can be accessed through prepulse inhibition (PPI) in humans [2,29,38] and rodents [3,36,37]. Schizophrenia patients exhibit heritable

* Corresponding author at: Department of Morphology Physiology and Basic Pathology, University of São Paulo, Dental School of Ribeirão Preto, Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), 14049-904, Brazil.
Tel.: +55 1636024047; fax: +55 16 36330999.
E-mail address: eadelbel@forp.usp.br (E.A. Del Bel).
[1] These authors contributed equally to this work.

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.11.026

deficits in the PPI response [2], and generally, in rodents, PPI deficit is pharmacologically induced through an increase of dopaminergic neurotransmission [3,36,43]. The dopaminergic (D1/D2) receptor agonist apomorphine induces a reduction in the PPI response of the acoustic startle reflex in rodents, which is a reliable index of the sensorimotor gating deficit [35]. The ability of antipsychotics drugs to restore the PPI disruption may be predictive of its antipsychotic effects [9]. Dopaminergic dysfunction remains the central pathophysiological theory of schizophrenia (for review see [15]), however, the schizophrenia physiopathology might also be related to a brain development and plasticity disorder. In this case, the activity and excitability of multiple brain regions including hippocampus and substantia nigra, may be strongly altered [33,34].

Evidence for the hippocampal involvement in the neuropathology of schizophrenia has been found in humans, from in vivo neuropsychology, structural and functional imaging, and also from *post mortem* histological, morphometric and genetic analyses [14]. Specific evidence for the hippocampal regulation of PPI comes from experimental animal studies [5,39]. Recently, K^+ channels have been proposed to play a role in the mechanisms of neural plasticity which are altered in various psychiatric disorders, especially in hippocampus [16]. The dentate gyrus of the hippocampus acts as the "gate keeper" or the "filter" of the hippocampal function [10]. It has been described that dopamine modulates the activity of new dentate granule cells in the dentate gyrus [25]. Also, dopamine acts as a gate on the direct cortical input to the hippocampus, modulating synaptic plasticity and information flow in a frequency-dependent manner [17]. In this context, Eag1 K^+ channel expression in the dentate gyrus of hippocampal neurons [7] becomes interesting.

Because of the lack of specific pharmacological instruments, Eag1 monoclonal antibody may provide an attractive tool to elucidate the functional role of this channel in mammalian brain [24]. Monoclonal antibodies represent a strategy to generate highly selective inhibitors against cell surface molecules, enabling a specific antigen to be distinguished from its close homologues [12,31]. A specific Eag1 antibody was validated and described as the first monoclonal antibody that selectively inhibits a K^+ current in intact cells [12]. Taking advantage of the specificity of the recombinant anti-Eag1 single-chain antibody, and the singular distribution of Eag1 in the hippocampus (Fig. 1) [7] we investigate the effects of Eag1 antibody microinjection into the dentate gyrus of rats after systemic apomorphine treatment.

2. Materials and methods

2.1. Animals

Male *Wistar* rats ($n = 11$; 250–300 g) were used. The experimental protocol followed the guidelines for the care and use of mammals in Neuroscience and Behavioral Research (ILAR, USA). Rats were housed four per cage, under controlled temperature ($23 \pm 1\,^{\circ}C$) and light/dark cycle (12–12 h; lights on at 0600 hours) with food and water constantly available. Tests were performed in the light phase.

2.2. Drugs

Apomorphine (Sigma–Aldrich, Germany) was dissolved in distilled water with 0.1% ascorbic acid and injected subcutaneously (s.c.; 0.5 mg/kg) at 1 ml/kg. Eag1-specific recombinant anti-Eag1 single-chain antibody (1 μg/1 μl of water RNAse free) was bilaterally injected with 30 gauge needles (16 mm) into the dentate gyrus at a volume of 0.5 μL delivered over 60 s using a microdrive injection pump.

2.3. Sensorimotor evaluation

PPI refers to the reduction in the startle magnitude to a startling acoustic stimulus 'pulse' when it is shortly preceded by a weaker 'prepulse' stimulus [35]. Startle response and PPI were conducted simultaneously in two identical startle systems (Med Associates, Inc., USA) as described before [30].

2.3.1. Pre-test procedure

Rats were subjected to a PPI pre-test session previously to the surgery. All animals selected to conduct the study presented a positive response to the PPI and an average of startle amplitude of 589 ± 107 (arbitrary units).

2.3.2. Post-surgical test procedure

One week after surgery, animals were re-subjected to the PPI test (post-surgical analyses) before apomorphine treatment.

2.4. Surgery

Rats were anesthetized with ketamine/xylazine (10:7, 100 mg/kg; intraperitoneal) and placed in a stereotaxic apparatus. Stainless steel guide cannulae were bilaterally implanted 3 mm above the injection site within the dentate gyrus (anteroposterior, −4 mm; lateral, ±2.6 mm; dorso-ventral, −2.1 mm) [28]. The guide cannulae were kept unobstructed by dummy stylets.

2.5. Experimental design

After surgery for bilaterally hippocampus cannulae implantation all rats showed a significant decrease of their startle amplitude (compared to pre-test condition). Animals were tested repeatedly (pre-test, post-surgical apomorphine, and apomorphine + Eag1 K^+ channel antibody) with a minimum interval of 4 days, with exception of the post surgical test. PPI disruption was induced by acute apomorphine treatment. Microinjection of the anti-Eag1 K^+ channel antibody bilaterally in the dentate gyrus of hippocampus was conducted 20 min after the apomorphine treatment. Two rats were not included in the behavioral analyses (Fig. 2).

2.6. Statistical analyses

The acoustic startle response to pulse alone and to prepulse + pulse was analyzed by repeated measures analysis of variance (RM-ANOVA) with stimuli (four levels: pulse; 81 or 73 or 69 dB prepulse + pulse) as a within-subjects factor and condition (pre or post-surgical or pharmacological treatment; four levels) as between-subjects factors. For the mean %PPI, RM-ANOVA was conducted with intensity of prepulse (three levels) as a within-subject factor, and condition as a between-subjects factor. In the case of significant main effects the RM-ANOVA was followed by Duncan's test for post hoc comparisons ($P < 0.05$).

3. Results

3.1. Startle amplitude

We found a significant main effect of stimuli ($F(3,96) = 13.017$; $P = 0.000$) and condition ($F(3,32) = 6.48$; $P = 0.001$), but not a significant interaction between stimuli and condition ($F(9,96) = 1.866$; $P = 0.066$). Rats with bilateral cannulae implantation into the dentate gyrus showed a significant decrease in their startle amplitude to the pulse alone compared with the pre-test condition (Fig. 3). Apomorphine systemic treatment induced an increase in the startle amplitude, but this effect was not statistically significant. After Eag1 antibody bilaterally injected into the dentate gyrus of hippocampus

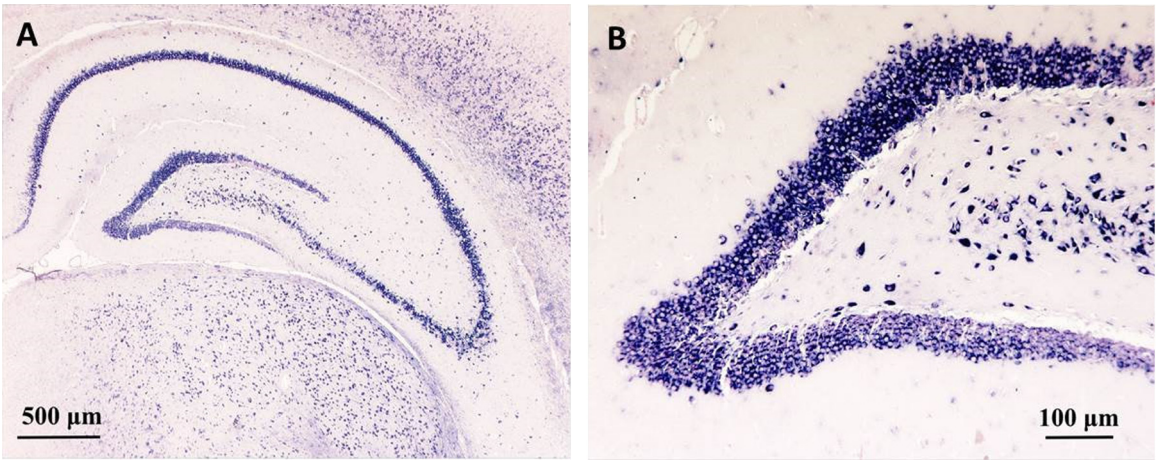


Fig. 1. Photomicrographs A and B showing Eag1 immunoreactivity in the rat hippocampus. The detection system (NBT/BCIP) produced an intense blue color mainly in the cell bodies.

the startle amplitude was significantly increased (bring to normal) compared with the post-surgical condition (post hoc Duncan; $P < 0.05$; Fig. 3). In the 81 and 73 dB prepulse + pulse trials the startle magnitude was significant lower than the respective stimulus of the pre-test condition. However, importantly, the startle amplitude to the pulse was higher than the startle amplitude to the prepulse + pulse (with all prepulse intensities) in the post surgical condition (Fig. 3).

3.2. Prepulse inhibition

There was a significant effect of condition ($F(3,32) = 4.10$; $P = 0.014$), but not of prepulse intensity ($F(2,64) = 0.185$; $P = 0.831$) or an interaction between prepulse intensity and condition ($F(6,64) = 1.105$; $P = 0.369$). Systemic treatment with apomorphine induced significant PPI disruption. Eag1 antibody injected bilaterally into the dentate gyrus did not modify this effect (post hoc Duncan; $P < 0.05$; Fig. 4). PPI on post-surgical condition was not different to the pre-test (data not shown).

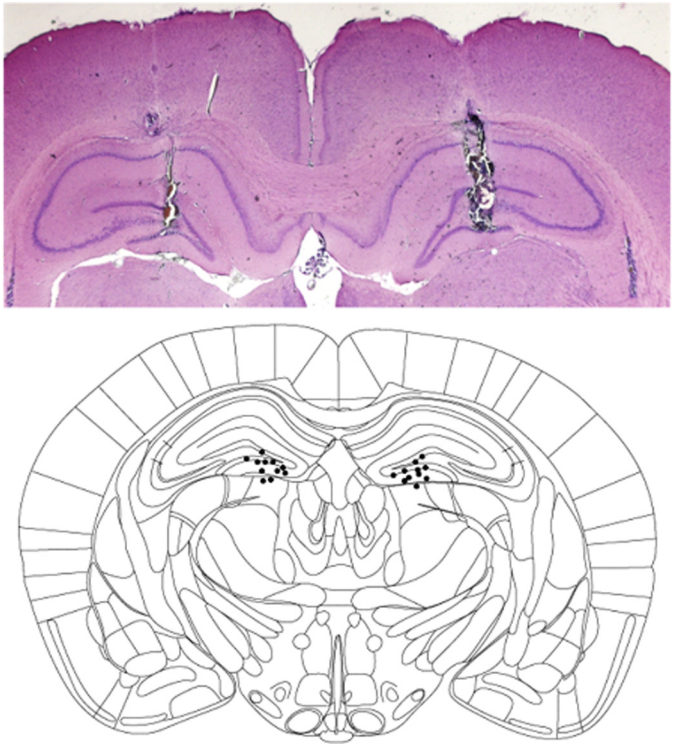


Fig. 2. Hematoxilin-eosin representative histological section and cannulae-tip placements schema within the dentate gyrus of hippocampus. Injection needle tips location within the dentate gyrus of hippocampus was determined according to the standardized plates – Bregma −2.06; interaural 1.74 mm [28]. Two animals within cannulae insertions outside the dentate gyrus were not included in data analyses.

4. Discussion

Dopamine system appears to be critical connected to the PPI modulation [36]. PPI response may be disrupted in schizophrenia patients [2,36], despite the fact that PPI impairment is observed in several other psychiatric disorders [2,9]. Clearly, the PPI deficit that is experimentally induced does not constitute an animal model of schizophrenia per se but appears to provide an applicable model of sensorimotor gating deficit [9,25]. The antipsychotic drugs used to treat schizophrenia symptoms share the pharmacological property of dopamine D2 receptor antagonism [20]. It was suggested, however, that the therapeutic action of antipsychotic drugs could be in addition dependent on the presynaptic ERG K^+ channel inhibition [6,32,40]. We investigate the ability of an Eag1 K^+ channel antibody microinjected into the dentate gyrus of hippocampus to attenuate the apomorphine-induced PPI disruption. Bilateral injection of

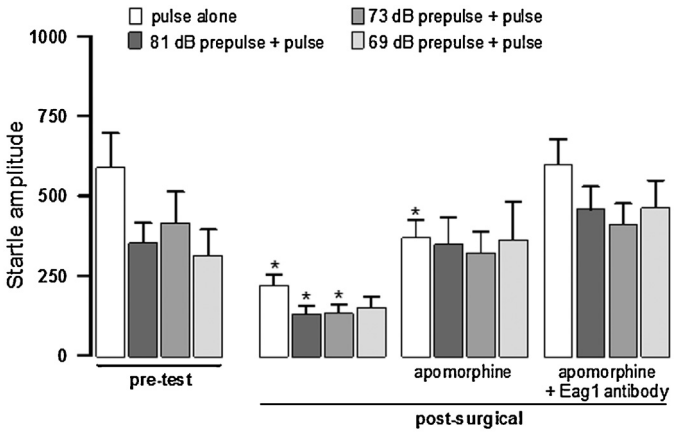


Fig. 3. Effects of Eag1 K^+ channels antibody on the startle amplitude. Animals showed significant decrease in their startle amplitude to pulse alone after surgery. Apomorphine treatment induced an increase in the startle response, but this effect was not statistically significant. The Eag1 K^+ channels antibody bilaterally injected in the dentate gyrus of hippocampus restored the startle amplitude. $^*P < 0.05$ compared with the respective stimulus of the pre-test condition. Data represent means ± SEM. RM-ANOVA, post hoc Duncan ($P < 0.05$; $n = 9$).

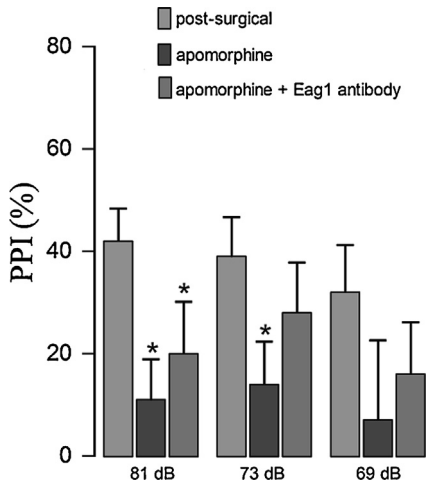


Fig. 4. Effects of Eag1 K^+ channels antibody in the PPI disruption induced by apomorphine. Eag1 K^+ channels antibody bilaterally injected on dentate gyrus of hippocampus did not modify the PPI-disruptive effect of apomorphine (prepulse intensities of 73 and 81 dB). *$P < 0.05$ compared with post-surgical condition. Data represent means ± SEM. RM-ANOVA, post hoc Duncan ($P < 0.05$; $n = 9$).

Eag1 antibody (0.5 μg data not shown; or 1.0 μg) into the dentate gyrus did not modify apomorphine-disruptive effects in the PPI, but reversed the decreased startle amplitude measured after surgery.

No physiological function for the Eag1 K^+ channels in the central nervous system has been reported so far for mammals. Recently, no difference in the PPI disruption induced by apomorphine in Eag1 knockout animals was found, corroborating with our results [41]. However, these authors demonstrate that Eag1 knockout mice ($K_v10.1^{-/-}$) show an increased reactivity to apomorphine treatment in the PPI test after amphetamine sensitization, and a significant increase in the responsiveness to the haloperidol in the catalepsy test. The authors suggested that $K_v10.1^{-/-}$ mice show a hyperreactivity of the dopaminergic system, or a decreased density/number of the dopaminergic receptors [41].

It was impossible to disclose the reason for decreasing startle amplitude after the hippocampal cannulae implantation. Despite the fact that startle reflex is sensitive to habituation, and may reflect hearing loss, these do not appear the reasons for the startle decrease. Zhang and co-workers conducted several studies using an extensive number of drug-free rats with dorsal or ventral hippocampal-cannulation [1,44–46], but these authors did not describe any startle reflex impairment. Contrasting, it has been reported the impact of different manipulations on ventral or dorsal hippocampus in the startle reactivity [45,46]. In addition, Zhang and co-workers [46] suggested that these effects in the startle reactivity may be mediated through the hippocampal projections to the amygdala or to the bed nucleus of the stria terminalis, which have access to the brain stem startle circuit [21]. Primary acoustic startle pathway involves few synapses including the cochlear root neurons, neurons in the nucleus reticularis pontis caudalis, and motoneurons in the spinal cord [22]. Since the startle reflex is high sensitive to habituation, sensitization, sensorimotor gating, and affective modulation, it might be used to study several conditions including fear and anxiety, affective disturbances, motivational states, and homeostasis [13]. Undoubtedly, Eag1 K^+ channel blockade effects in the startle response merits further investigation.

Contrasting, consistent with Swerdlow and co-workers [35] we should carefully interpreting treatment effects in the PPI response in the presence of parallel effects on startle amplitude. Consistent with these authors it is possible that in the presence of a reduction in the startle magnitude in pulse-alone trials it is difficult to determine whether the lack of a comparable reduction in startle magnitude in prepulse + pulse trials reflects a reduction in sensorimotor gating, or a 'floor' effect in the prepulse + pulse trials. In the same way, an increase in startle magnitude of both pulse-alone trials and prepulse + pulse trials could reflects 'ceiling' effects, rather than a reduction in sensorimotor gating. However, despite the effects of surgical procedure in the startle amplitude, our data demonstrate the ability of apomorphine to reduce PPI, as described before, even in the presence of apomorphine effects in startle amplitude [4,35]. If the absence of Eag1 blockade effects in the PPI response was influenced by its effects in the startle amplitude is not possible to determine via these data alone.

5. Conclusion

Eag1 K^+ channels blockade modified the startle response without robustly affecting the apomorphine-disruptive effects in the PPI. We provide the first demonstration of the possible influence of these channels in the startle response, which may represent a biological important phenomenon. Although our results do not support the classical antipsychotic-like effects to the Eag1 K^+ channels blockade data merits further studies.

Acknowledgements

We would like to thank Célia Ap. da Silva for the technical support, and to Nadia Rubia Ferreira (PhD) which friendly gave us the Eag1 K^+ channels immunohistochemistry photomicrographs. This research was supported by CNPq Brazil and CAPES/DAAD.

References

[1] T. Bast, W.N. Zhang, C. Heidbreder, J. Feldon, Hyperactivity and disruption of prepulse inhibition induced by N-methyl-D-aspartate stimulation of the ventral hippocampus and the effects of pretreatment with haloperidol and clozapine, Neuroscience 103 (2001) 325–335.
[2] D.L. Braff, M.A. Geyer, N.R. Swerdlow, Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies, Psychopharmacology (Berlin) 156 (2001) 234–258.
[3] M.R. Breier, B. Lewis, J.M. Shoemaker, G.A. Light, N.R. Swerdlow, Sensory and sensorimotor gating-disruptive effects of apomorphine in Sprague Dawley and Long Evans rats, Behav. Brain Res. 208 (2010) 560–565.
[4] J. Brosda, L. Hayn, C. Klein, M. Koch, C. Meyer, R. Schallhorn, N. Wegener, Pharmacological and parametrical investigation of prepulse inhibition of startle and prepulse elicited reactions in Wistar rats, Pharmacol. Biochem. Behav. 99 (2011) 22–28.
[5] S.B. Caine, M.A. Geyer, N.R. Swerdlow, Carbachol infusion into the dentate gyrus disrupts sensorimotor gating of startle in the rat, Psychopharmacology (Berlin) 105 (1991) 347–354.
[6] V. Calderone, L. Testai, E. Martinotti, M. Del Tacca, M.C. Breschi, Drug-induced block of cardiac HERG potassium channels and development of torsade de pointes arrhythmias: the case of antipsychotics, J. Pharm. Pharmacol. 57 (2005) 151–161.
[7] N.R. Ferreira, M. Mitkovski, W. Stühmer, L.A. Pardo, E.A. Del Bel, Ether-à-go-go 1 (Eag1) potassium channel expression in dopaminergic neurons of basal ganglia is modulated by 6-hydroxydopamine lesion, Neurotox. Res. 21 (2012) 317–333.
[8] R.V. Frolov, A. Bagati, B. Casino, S. Singh, Potassium channels in Drosophila: historical breakthroughs, significance, and perspectives, J. Neurogenet. 26 (2012) 275–290.
[9] M.A. Geyer, K. Krebs-Thomson, D.L. Braff, N.R. Swerdlow, Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review, Psychopharmacology (Berlin) 156 (2001) 117–154.
[10] N. Guo, K. Yoshizaki, R. Kimura, F. Suto, Y. Yanagawa, N. Osumi, A sensitive period for GABAergic interneurons in the dentate gyrus in modulating sensorimotor gating, J. Neurosci. 33 (2013) 6691–6704.
[11] D. Gómez-Varela, T. Kohl, M. Schmidt, M.E. Rubio, H. Kawabe, R.B. Nehring, S. Schäfer, W. Stühmer, L.A. Pardo, Characterization of Eag1 channel lateral mobility in rat hippocampal cultures by single-particle-tracking with quantum dots, PLoS One 5 (2010) e8858.
[12] D. Gómez-Varela, E. Zwick-Wallasch, H. Knötgen, A. Sánchez, T. Hettmann, D. Ossipov, R. Weseloh, C. Contreras-Jurado, M. Rothe, W. Stühmer, L.A. Pardo, Monoclonal antibody blockade of the human Eag1 potassium channel function exerts antitumor activity, Cancer Res. 67 (2007) 7343–7349.

[13] C. Grillon, J. Baas, A review of the modulation of the startle reflex by affective states and its application in psychiatry, Clin. Neurophysiol. 114 (2003) 1557–1579.
[14] P.J. Harrison, The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications, Psychopharmacology (Berlin) 174 (2004) 151–162.
[15] O.D. Howes, S. Kapur, The dopamine hypothesis of schizophrenia: version III – the final common pathway, Schizophr. Bull. 35 (2009) 549–562.
[16] P. Imbrici, D.C. Camerino, D. Tricarico, Major channels involved in neuropsychiatric disorders and therapeutic perspectives, Front. Genet. 4 (2013) 76.
[17] H.T. Ito, E.M. Schuman, Frequency-dependent gating of synaptic transmission and plasticity by dopamine, Front. Neural Circuits 1 (2007) 1.
[18] C.J. Jeng, C.C. Chang, C.Y. Tang, Differential localization of rat Eag1 and Eag2 K^+ channels in hippocampal neurons, Neuroreport 16 (2005) 229–233.
[19] M. Ju, D. Wray, Molecular identification and characterisation of the human eag2 potassium channel, FEBS Lett. 524 (2002) 204–210.
[20] S. Kapur, P. Seeman, Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? A new hypothesis, Am. J. Psychiatry 158 (2001) 360–369.
[21] M. Koch, The neurobiology of startle, Prog. Neurobiol. 59 (1999) 107–128.
[22] Y. Lee, D.E. López, E.G. Meloni, M. Davis, A primary acoustic startle pathway: obligatory role of cochlear root neurons and the nucleus reticularis pontis caudalis, J. Neurosci. 16 (1996) 3775–3789.
[23] J. Ludwig, R. Weseloh, C. Karschin, Q. Liu, R. Netzer, B. Engeland, C. Stansfeld, O. Pongs, Cloning and functional expression of rat eag2, a new member of the ether-à-go-go family of potassium channels and comparison of its distribution with that of eag1, Mol. Cell. Neurosci. 16 (2000) 59–70.
[24] S. Martin, C. Lino de Oliveira, F. Mello de Queiroz, L.A. Pardo, W. Stühmer, E. Del Bel, Eag1 potassium channel immunohistochemistry in the CNS of adult rat and selected regions of human brain, Neuroscience 155 (2008) 833–844.
[25] Y. Mu, C. Zhao, F.H. Gage, Dopaminergic modulation of cortical inputs during maturation of adult-born dentate granule cells, J. Neurosci. 31 (2011) 4113–4123.
[26] T. Occhiodoro, L. Bernheim, J.H. Liu, P. Bijlenga, M. Sinnreich, C.R. Bader, J. Fischer-Lougheed, Cloning of a human ether-à-go-go potassium channel expressed in myoblasts at the onset of fusion, FEBS Lett. 434 (1998) 177–182.
[27] L.A. Pardo, D. del Camino, A. Sánchez, F. Alves, A. Brüggemann, S. Beckh, W. Stühmer, Oncogenic potential of EAG K(+) channels, EMBO J. 18 (1999) 5540–5547.
[28] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, Academic Press, San Diego, 1997.
[29] W. Perry, D. Feifel, A. Minassian, I. Bhattacharjie, D.L. Braff, Information processing deficits in acutely psychotic schizophrenia patients medicated and unmedicated at the time of admission, Am. J. Psychiatry 159 (2002) 1375–1381.
[30] C. Salum, A.C. Issy, M.L. Brandão, F.S. Guimarães, E.A. Bel, Nitric oxide modulates dopaminergic regulation of prepulse inhibition in the basolateral amygdala, J. Psychopharmacol. 25 (2011) 1639–1648.
[31] A. Sharma, H.S. Sharma, Monoclonal antibodies as novel neurotherapeutic agents in CNS injury and repair, Int. Rev. Neurobiol. 102 (2012) 23–45.
[32] P.D. Shepard, C.C. Canavier, E.S. Levitan, Ether-à-go-go-related gene potassium channels: what's all the buzz about? Schizophr. Bull. 33 (2007) 1263–1269.
[33] C. Silveira, J. Marques-Teixeira, A.J. de Bastos-Leite, More than one century of schizophrenia: an evolving perspective, J. Nerv. Ment. Dis. 200 (2012) 1054–1057.
[34] M.K. Stachowiak, A. Kucinski, R. Curl, C. Syposs, Y. Yang, S. Narla, C. Terranova, D. Prokop, I. Klejbor, M. Bencherif, B. Birkaya, T. Corso, A. Parikh, E.S. Tzanakakis, S. Wersinger, E.K. Stachowiak, Schizophrenia: a neurodevelopmental disorder – integrative genomic hypothesis and therapeutic implications from a transgenic mouse model, Schizophr. Res. 143 (2013) 367–376.
[35] N.R. Swerdlow, D.L. Braff, M.A. Geyer, Animal models of deficient sensorimotor gating: what we know, what we think we know, and what we hope to know soon, Behav. Pharmacol. 11 (2000) 185–204.
[36] N.R. Swerdlow, D.L. Braff, M.A. Geyer, G.F. Koob, Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics, Biol. Psychiatry 21 (1986) 23–33.
[37] N.R. Swerdlow, D.L. Braff, N. Taaid, M.A. Geyer, Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients, Arch. Gen. Psychiatry 51 (1994) 139–154.
[38] N.R. Swerdlow, A. Eastvold, B. Karban, Y. Ploum, N. Stephany, M.A. Geyer, K. Cadenhead, P.P. Auerbach, Dopamine agonist effects on startle and sensorimotor gating in normal male subjects: time course studies, Psychopharmacology (Berlin) 161 (2002) 189–201.
[39] N.R. Swerdlow, G.A. Light, M.R. Breier, J.M. Shoemaker, R.L. Saint Marie, A.C. Neary, M.A. Geyer, K.E. Stevens, S.B. Powell, Sensory and sensorimotor gating deficits after neonatal ventral hippocampal lesions in rats, Dev. Neurosci. 34 (2012) 240–249.
[40] L. Testai, A.M. Bianucci, I. Massarelli, M.C. Breschi, E. Martinotti, V. Calderone, Torsadogenic cardiotoxicity of antipsychotic drugs: a structural feature, potentially involved in the interaction with cardiac HERG potassium channels, Curr. Med. Chem. 11 (2004) 2691–2706.
[41] R. Ufartes, T. Schneider, L.S. Mortensen, C. de Juan Romero, K. Hentrich, H. Knoetgen, V. Beilinson, W. Moebius, V. Tarabykin, F. Alves, L.A. Pardo, J.N. Rawlins, W. Stuehmer, Behavioural and functional characterization of Kv10.1 (Eag1) knockout mice, Hum. Mol. Genet. 22 (11) (2013) 2247–2262.
[42] J.W. Warmke, B. Ganetzky, A family of potassium channel genes related to eag in Drosophila and mammals, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 3438–3442.
[43] J. Zhang, C. Forkstam, J.A. Engel, L. Svensson, Role of dopamine in prepulse inhibition of acoustic startle, Psychopharmacology (Berlin) 149 (2000) 181–188.
[44] W.N. Zhang, T. Bast, J. Feldon, Effects of hippocampal N-methyl-D-aspartate infusion on locomotor activity and prepulse inhibition: differences between the dorsal and ventral hippocampus, Behav. Neurosci. 116 (2002) 72–84.
[45] W.N. Zhang, T. Bast, J. Feldon, Microinfusion of the non-competitive N-methyl-D-aspartate receptor antagonist MK-801 (dizocilpine) into the dorsal hippocampus of wistar rats does not affect latent inhibition and prepulse inhibition, but increases startle reaction and locomotor activity, Neuroscience 101 (2000) 589–599.
[46] W.N. Zhang, T. Bast, J. Feldon, Prepulse inhibition in rats with temporary inhibition/inactivation of ventral or dorsal hippocampus, Pharmacol. Biochem. Behav. 73 (2002) 929–940.