Pharmacology, Biochemistry and Behavior 93 (2009) 363–367

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Topiramate antagonizes NMDA- and AMPA-induced seizure-like activity in planarians

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ARTICLE INFO

Article history:
Received 21 October 2008
Received in revised form 6 May 2009
Accepted 7 May 2009
Available online 15 May 2009

Keywords:
Topiramate
Glutamate receptors
Planarians
NMDA
AMPA
MK-801

ABSTRACT

The mechanism of anticonvulsant action of topiramate includes inhibition of glutamate-activated ion channels. The evidence is most convincing for direct inhibitory action at the ionotropic AMPA (α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and kainate ((2*S*,3*S*,4*S*)-3-(Carboxymethyl)-4-prop-1-en-2-ylpyrrolidine-2-carboxylic acid) glutamate receptor subtypes. Less direct connection has been made to the NMDA (*N*-Methyl-D-aspartate) subtype. In the present study, we demonstrate that NMDA and AMPA produce concentration-dependent seizure-like activity in planarians, a type of flatworm which possesses mammalian-like neurotransmitters. In contrast, planarians exposed to the inhibitory amino acid, glycine, did not display *p*SLA. For combination experiments, topiramate significantly reduced planarian seizure-like activity (*p*SLA) produced by NMDA or AMPA. Additionally, NMDA-induced *p*SLA was antagonized by either an NMDA receptor antagonist (MK-801) or AMPA receptor antagonist (DNQX), thus suggesting that NMDA-induced *p*SLA was mediated by NMDA and non-NMDA receptors. The present results provide pharmacologic evidence of a functional inhibitory action of topiramate on glutamate receptor activity in invertebrates and provide a sensitive, quantifiable end-point for studying anti-seizure pharmacology.

1. Introduction

Topiramate (2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate) is a wide-spectrum sulfamate-substituted monosaccharide anticonvulsant used as mono- or adjunctive therapy (Maryanoff et al., 1987). Originally thought to work *via* inhibition of carbonic anhydrase (Shank et al., 1994, 2005, 2006; Dodgson et al., 2000), it is now believed that several mechanisms contribute to its anticonvulsant activity. The four major putative mechanisms involve an action on ionotropic receptors (voltage, glutamate, and GABA-activated ion channels) (White et al., 1995, 1997, 2000; Zona et al., 1997; Taverna et al., 1999; Wu et al., 1999; DeLorenzo et al., 2000; Gordey et al., 2000; McLean et al., 2000; Zhang et al., 2000; Herrero et al., 2002; Curia et al., 2004; McNaughton et al., 2004; Russo and Constanti, 2004; Kuzmiski et al., 2005; Okada et al., 2005a,b; Leppik et al., 2006; Simeone et al., 2006; Sun et al., 2007; reviewed in Shank and Maryanoff, 2008). There is convincing evidence that topiramate has inhibitory effects on the ionotropic glutamate AMPA and kainate (GluR5) (Gibbs et al., 2000; Skradski and White, 2000; Gryder and Rogawski, 2003; Qian and Noebels, 2003; Angehagen et al., 2004, 2005; Poulsen et al., 2004) receptor subtypes. Topiramate has been reported to lack direct effect on NMDA receptors. However, NMDA receptor subtype activity is known to be influenced by AMPA receptor activity (Kim et al., 2007; Du et al., 2008). It thus seems possible that topiramate might be able to affect an NMDA-induced behavior, particularly in a simple model. Planarians provide such a model (summarized in Raffa and Rawls, 2008). We previously demonstrated the presence of glutamate (mean = 323 ± 44 pmol/mg-animal) in planarians (Rawls et al., 2006). Planarians also express the genes for at least two types of ionotropic glutamate receptors which share high sequence similarity to neural specific genes isolated from humans and mice (Cebrià et al., 2002). Thus, the present study determined if planarians exposed to NMDA or AMPA display seizure-like activity and, if so, whether or not topiramate is capable of blocking planarian seizure-like activity (*p*SLA) induced by these glutamatergic agents.

2. Methods

2.1. Animals and drugs

Planarians (*Dugesia dorotocephala*) were purchased from Carolina Biological Supply (Burlington, NC, USA), acclimated to room temperature (21 °C), and tested within 3 days of receipt. NMDA, glycine, (+)-MK 801 maleate (MK-801), (*RS*)-AMPA, and 6,7-Dinitroquinoxaline-2,3-dione disodium salt (DNQX) were purchased from Tocris Biosciences (St. Louis, MO). Topiramate was purchased from Toronto Research Chemicals (North York, Ontario). (*S*)-(−)-Propranolol hydrochloride was purchased from Sigma-Aldrich (St. Louis. MO). Stock solutions of each drug were prepared daily in tap water containing AmQuel® water conditioner. All treatment solutions were diluted with tap water containing AmQuel® water conditioner.

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doi:10.1016/j.pbb.2009.05.005

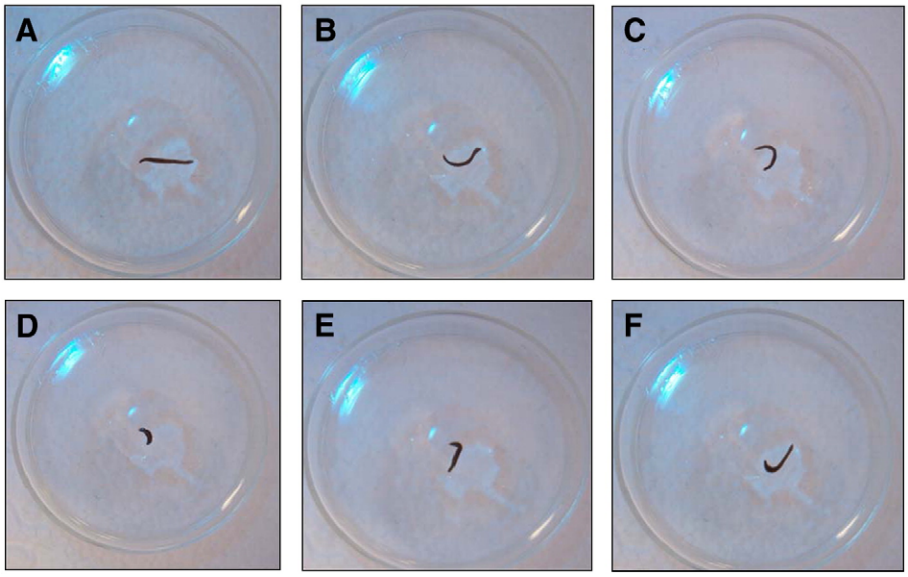

Fig. 1. A) Planarian exposed to water. B–F) *p*SLA during exposure to 3 mM NMDA.

2.2. Behavioral experiments

Planarian seizure-like activity (*p*SLA) was defined as asynchronous paroxysms (C-shape, twitching behaviors following pro-convulsant exposure) (Fig. 1). For each experiment, individual planarians were placed into a clear plastic petri dish (5.5 cm diameter) containing an agent or combination of agents and *p*SLA was then quantified as the number of behaviors displayed over a 5-min observation period. Dose combinations for each experiment are described in Table 1. Comparisons of cumulative group means (±S.E.M.) were evaluated by one-way ANOVA followed (if $p<0.05$) by a Dunnett's *post-hoc* analysis. Values of $p<0.05$ were considered to be statistically significant.

3. Results

3.1. NMDA produces pSLA

Planarians exposed to NMDA (15 mM) displayed recurrent seizure-like activity whereas glycine, another amino acid, did not produce *p*SLA during the 5-min observation interval Fig. 2 (inset). The onset of *p*SLA following NMDA exposure was rapid, occurring less than 10 s following drug application. Over the 5-min test period, the rate (i.e., number of behaviors in 1 min) of NMDA-induced *p*SLA was greatest during the first minute (approximately 24/min) and then became fairly constant over the last 3 min (approximately 8/min). The duration of each individual behavior was approximately 1 s. The effect of NMDA was concentration-dependent as planarians exposed to 1, 3 or 10 mM NMDA displayed significant *p*SLA (Fig. 2). Locomotor activity, although not quantified, was visibly reduced in planarians exposed to the higher concentrations (10 and 15 mM) of NMDA. The possibility that a lowering of the pH in the NMDA solutions contributed to the production of *p*SLA was investigated. The pH of the test water was 7.0, and the pH of a 3 mM NMDA solution was 6.6. Planarians exposed to only acetate buffer with a pH of 6.6 did not display *p*SLA. In fact, only when the pH of the acetate buffer was less than 5.0 did planarians display *p*SLA.

Table 1
Design for planarian seizure-like activity (*p*SLA) experiments.

Experiment	Drug(s)
1	NMDA (0.01, 0.1, 1, 3, 10 mM) or water
2	MK-801 (0, 0.1, 1, 3 mM) + NMDA (3 mM)
3	DNQX (0, 0.01, 0.1, 1, 3 mM) + NMDA (3 mM)
4	Topiramate (0, 0.1, 1, 3 mM) + NMDA (3 mM)
5	AMPA (0.01, 0.1, 1 mM) or water
6	Topiramate (0, 0.01, 0.1, 0.5, 1 mM) + AMPA (0.5 mM)

Each planarian was placed into a clear plastic petri dish (5.5 cm diameter) containing a drug or drug combination and then tested individually for *p*SLA for 5 min.

3.2. MK-801 or DNQX antagonizes NMDA-induced pSLA

The effects of progressively increasing concentrations of MK-801 (0,1, 1 or 3 mM) on *p*SLA induced by a fixed concentration of NMDA (3 mM) are presented in Fig. 3. All three concentrations of MK-801

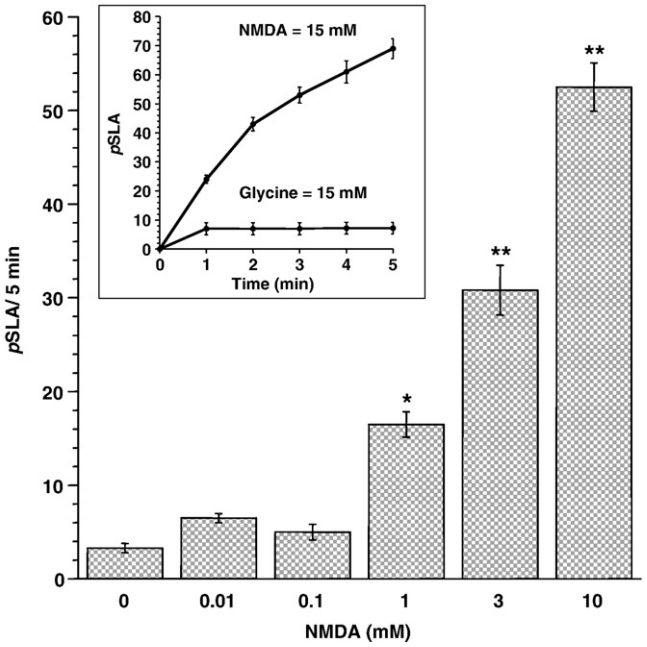

Fig. 2. NMDA (0.01–10 mM) produced concentration-related *p*SLA, expressed as the cumulative mean (±S.E.M.) over a 5-min observation period. *$p<0.05$ or **$p<0.01$ compared to control (0 mM NMDA). $N=8$–18 planarians per group. Inset) Effects of NMDA (15 mM) and glycine (15 mM) on *p*SLA, expressed as the number of occurrences (mean ± S.E.M.) each minute over a 5-min observation period. $N=5$–10 planarians per group.

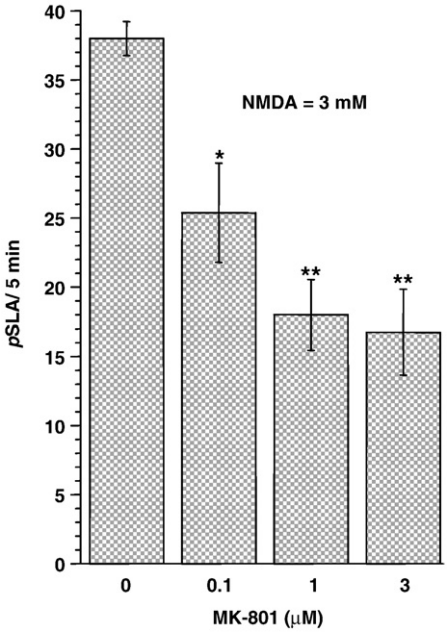

Fig. 3. Co-administration of MK-801 (0.1–3 μM) attenuated the *p*SLA produced by a fixed concentration of NMDA (3 mM). *$p<0.05$ or **$p<0.01$ compared to group treated with NMDA by itself. $N=8$–16 planarians per group.

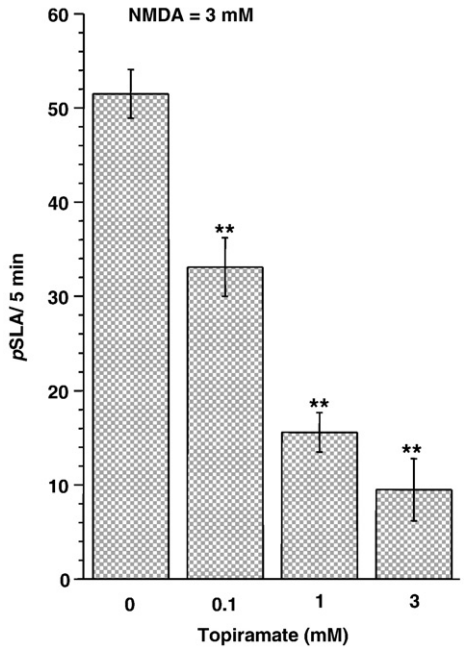

Fig. 5. Co-administration of topiramate (0.1–3 mM) attenuated the *p*SLA produced by a fixed concentration of NMDA (3 mM). **$p<0.01$ compared to group treated with NMDA by itself. $N=8$–18 planarians per group.

significantly reduced NMDA-induced *p*SLA. DNQX (0.01, 0.1, 1 or 3 mM) also produced a concentration-related inhibition of *p*SLA produced by 3 mM NMDA (Fig. 4). Planarians co-exposed to a solution containing NMDA (3 mM) and either 1 or 3 mM DNQX displayed significantly less *p*SLA than planarians exposed only to a solution containing NMDA (3 mM) ($p<0.01$). Planarians exposed only to MK-801 or DNQX did not display *p*SLA (data not shown).

3.3. Topiramate antagonizes pSLA induced by NMDA or AMPA

Effects of topiramate on *p*SLA induced by NMDA and AMPA are presented in Figs. 5 and 6, respectively. Planarians exposed only to topiramate did not display *p*SLA. For co-treatment experiments, planarians exposed to a combination of NMDA (3 mM) and topiramate (0.1, 1 or 3 mM) displayed significantly less *p*SLA than planarians exposed only to NMDA (3 mM) ($p<0.01$) (Fig. 5). AMPA (0.01, 0.1 or 1 mM) produced a concentration-related increase in *p*SLA (Fig. 6A). On the basis of those results, a concentration of 0.5 mM AMPA was then selected for combination experiments with topiramate. A combination of AMPA (0.5 mM) and topiramate (0.1, 1 or 3 mM) produced significantly less *p*SLA than AMPA (0.5 mM) by itself ($p<0.01$) (Fig. 6B). Propranolol, a drug that is not known to display anti-seizure properties in mammals, was used as a negative control for our topiramate experiments. When given in combination with either NMDA (3 mM) or AMPA (0.5 mM), propranolol (10 mM) did not produce a significant reduction in *p*SLA compared to planarians treated only with NMDA (3 mM) or AMPA (0.5 mM) ($p>0.05$) (data not shown).

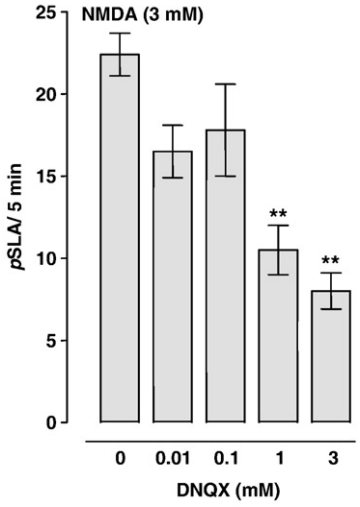

Fig. 4. Co-administration of DNQX (0.01–3 mM) attenuated the *p*SLA produced by a fixed concentration of NMDA (3 mM). **$p<0.01$ compared to group treated with NMDA by itself. $N=8$–20 planarians per group.

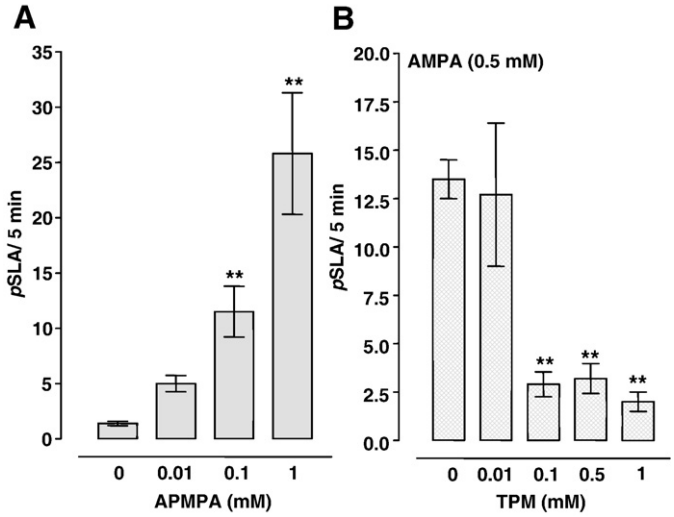

Fig. 6. A) AMPA (0.01–1 mM) produced concentration-related *p*SLA, expressed as the cumulative mean (±S.E.M.) over a 5-min observation period. **$p<0.01$ compared to control (0 mM AMPA). $N=6$–12 planarians per group. B) Co-administration of topiramate (0.01–1 mM) attenuated the *p*SLA produced by a fixed concentration of NMDA (3 mM). **$p<0.01$ compared to group treated with AMPA by itself. $N=8$–20 planarians per group.

4. Discussion

Excitotoxicity linked to excess glutamate activity has been implicated in the etiology, initiation, maintenance, and/or pathophysiological sequelae of epilepsy. Glutamate, the excitatory amino acid most abundant in mammalian central nervous system, is released in large quantities during seizures and triggers excitotoxic ion fluxes that are mediated or modulated by glutamate receptor subtypes. Fast excitatory glutamate neurotransmission involves ionotropic glutamate receptors, including AMPA and NMDA receptors, whereas slow responses involve metabatropic G protein-coupled glutamate receptors (see Bazan et al., 2002) and kainate produces a model of human temporal lobe epilepsy in animals (see Furuta et al., 2003). In the present study, planarians exposed to NMDA or AMPA displayed seizure-like activity that was antagonized by topiramate. These results provide pharmacologic evidence in favor of an antagonistic action of topiramate on seizure-like activity induced by NMDA, as well as AMPA.

Prior studies using neurochemical, molecular and behavioral approaches reveal that planarians utilize endogenous glutamate and express glutamate-like receptors. Our laboratory used HPLC to demonstrate that planarians contain endogenous glutamate and GABA, the principal inhibitory neurotransmitter in the mammalian brain (Rawls et al., 2006). Another study from our laboratory showed that an NMDA receptor antagonist, LY 235959, significantly reduces cannabinoid withdrawal in planarians (Rawls et al., 2007). From a molecular perspective, planarians do express genes for at least two types of ionotropic glutamate receptors which share high sequence similarity to neural specific genes isolated from humans and mice (Cebrià et al., 2002). Even though these results suggest that glutamate-like receptors are important factors in planarian physiology, they are clearly not identical to mammalian glutamate receptors. These differences in receptor homology and function may result in pharmacological effects that are not entirely the same across planarians and mammals. A related finding in our study is that a saturating concentration of MK-801 failed to completely antagonize NMDA-induced seizure-like activity. These data suggest a role for both NMDA-dependent and -independent processes in the seizure-like effects of NMDA in planarians. This interpretation was confirmed by the effect of the AMPA/kainate antagonist DNQX, which, akin to MK-801, antagonized a significant proportion of NMDA-induced seizure-like activity. Hence, in planarians, NMDA appears to produce seizure-like activity through NMDA and non-NMDA receptor activation.

The present study also demonstrated that topiramate antagonizes seizure-like activity produced by both NMDA and AMPA. While the inhibitory action of topiramate on the effect of AMPA in planarians is consistent with its documented action in mammals, few studies have investigated a role for topiramate in NMDA receptor pharmacology. For example, mammalian studies have shown that topiramate exerts inhibitory effects on the AMPA and kainate receptor subtypes (*e.g.*, Gibbs et al., 2000; Gryder and Rogawski, 2003) but has no direct effect on NMDA receptors (Qian and Noebels, 2003; Angehagen et al., 2004). However, it has been postulated (Angehagen et al., 2004, 2005) that topiramate "… binds to some vacant phosphorylation sites within one or more proteins that comprise the AMPA or kainate receptor complexes, and thereby prevents phosphorylation, and may exert allosteric modulatory effects on channel activity" (Shank and Maryanoff, 2008). By such a mechanism, topiramate could affect NMDA receptor activity through its effect on AMPA receptors. Our evidence suggests that topiramate, at least in planarians, is capable of inhibiting biological responses produced by agonists of NMDA and AMPA receptors. The effectiveness of topiramate on NMDA- and AMPA-induced effects in our model may be due to two factors, the (1) pharmacological diversity of the agent itself and (2) ability of NMDA to produce seizure-like activity through NMDA and non-NMDA receptor-dependent processes. Regarding the former point, the antiepileptic effect of topiramate is mediated by several processes, such as inhibition of inward currents at AMPA/kainate receptors, modification of sodium ion- and/or calcium ion-dependent action potentials, and enhancement of GABA-mediated chloride ion fluxes into neurons (Pappalardo et al., 2004; Ziemann, 2003; Nakamura et al., 2000; Shank et al., 2000). Hence, it is conceivable that the ability of topiramate to disrupt at least two processes that contribute to seizure-like activity (i.e., inhibition of AMPA- and NMDA-induced seizure-like activity) accounts for its broad effectiveness in planarians (Shank and Maryanoff, 2008).

In summary, the present results demonstrated that planarians exposed to NMDA or AMPA display *p*SLA. The antiepileptic drug topiramate antagonized *p*SLA produced by both agents. In addition to the immediate results, this study provides a sensitive and quantifiable *in vivo* endpoint for the study of seizure-inducing and seizure-inhibiting compounds and, further, provides the opportunity for the study of mechanistic questions related to pro- and anticonvulsant neurotransmitters and drugs.

Acknowledgements

This work was supported by NIH (NIDA) grants DA15378 (RBR) and DA022694 (SMR). The authors thank Timothy Schickley, Ph.D., for the suggestion of Planaria as a test model.

References

Angehagen M, Ben-Menachem E, Shank R, Ronnback L, Hansson E. Topiramate modulation of kainate-induced calcium currents is inversely related to channel phosphorylation level. J Neurochem 2004;88:320–5.
Angehagen M, Ronnback L, Hansson E, Ben-Menachem E. Topiramate reduces AMPA-induced Ca^{2+} transients and inhibits GluR1 subunit phosphorylation in astrocytes from primary cultures. J Neurochem 2005;94:1124–30.
Bazan NG, Tu B, Rodriguez de Turco EB. What synaptic lipid signaling tells us about seizure-induced damage and epileptogenesis. Prog Brain Res 2002;135:175–85.
Cebrià F, Kudome T, Nakazawa M, Mineta K, Ikeo K, Gojobori T, et al. The expression of neural-specific genes reveals the structural and molecular complexity of the planarian central nervous system. Mech Dev 2002;116:199–204.
Curia G, Aracri P, Sancini G, Mantegazza M, Avanzini G, Franceschetti S. Protein-kinase C-dependent phosphorylation inhibits the effect of the antiepileptic drug topiramate on the persistent fraction of sodium currents. Neuroscience 2004;127:63–8.
DeLorenzo RJ, Sombati S, Coulter DA. Effects of topiramate on sustained repetitive firing and spontaneous recurrent seizure discharges in cultured hippocampal neurons. Epilepsia 2000;41(Suppl.1):S40–4.
Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isozymes. Epilepsia 2000;41(Suppl.1):S35–9.
Du J, Creson TK, Wu LJ, Ren M, Gray NA, Falke C, et al. The role of hippocampal GluR1 and GluR2 receptors in manic-like behavior. J Neurosci 2008;28:68–79.
Furuta A, Noda M, Suzuki SO, Goto Y, Kanahori Y, Rothstein JD, et al. Translocation of glutamate transporter subtype excitatory amino acid carrier 1 protein in kainic acid-induced rat epilepsy. Am J Pathol 2003;163:779–87.
Gibbs III JW, Sombati S, DeLorenzo RJ, Coulter DA. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 2000;41(Suppl.1):S10–6.
Gordey M, DeLorey TM, Olsen RW. Differential sensitivity of recombinant $GABA_A$ receptors expressed in *Xenopus* oocytes to modulation by topiramate. Epilepsia 2000;41(Suppl.1):S25–9.
Gryder DS, Rogawski MA. Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. J Neurosci 2003;23:7069–74.
Herrero AI, DelOlmo N, Gonzalez-Escalada JR, Solis JM. Two new actions of topiramate: inhibition of depolarizing $GABA_A$-mediated responses and activation of a potassium conductance. Neuropharmacology 2002;42:210–20.
Kim MJ, Fytai K, Jo J, Hayashi Y, Cho K, Sheng M. Synaptic accumulation of PSD-95 and synaptic function regulated by phosphorylation of serine-295 of PSD-95. Neuron 2007;56:488–502.
Kuzmiski JB, Barr W, Zamponi GW, MacVicar BA. Topiramate inhibits the initiation of plateau potentials in CA1 neurons by depressing R-type calcium channels. Epilepsia 2005;46:481–9.
Leppik IE, Kelly KM, deToledo-Morrell L, Patrylo PR, DeLorenzo RJ, Mathern GW, et al. Basic research in epilepsy and aging. Epilepsy Res 2006;68S:S21-37.
Maryanoff BE, Nortey SO, Gardocki JF, Shank RP, Dodgson SP. Anticonvulsant *O*-alkyl sulfamates, 23:45-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate and related compounds. J Med Chem 1987;30:880–7.
McLean MJ, Bukhari AA, Wamil AW. Effects of topiramate on sodium-dependent action potential firing by mouse spinal cord neurons in cell culture. Epilepsia 2000;41(Suppl.1):S21–4.
McNaughton NC, Davies CH, Randall A. Inhibition of α_{1E} Ca^{2+} channels by carbonic anhydrase inhibitors. J Pharmacol Sci 2004;95:240–7.
Nakamura J, Kuwana Y, Yukitoshi N. Target pharmacology of topiramate, a new antiepileptic drug. Nippon Yakurigaku Zasshi 2000;115:53–7.

Okada M, Zhu G, Yoshida K, Kanaia K, Hirosec S, Kanekoa S. Exocytosis mechanism as a new targeting site for mechanisms of action of antiepileptic drugs. Life Sci 2005a;72: 465–73.

Okada M, Yoshida S, Zhu G, Hirosec S, Kanekoa S. Biphasic actions of topiramate on monoamine exocytosis associated with both soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors and Ca^{2+}-induced Ca^{2+}-releasing systems. Neuroscience 2005b;134:233–46.

Pappalardo A, Liberto A, Patti F, Reggio A. Neuroprotective effects of topiramate. Clin Ter 2004;155:75–8.

Poulsen CF, Simeone TA, Maar TE, Smith-Swintosky V, White HS, Schousboe A. Modulation by topiramate of AMPA and kainate mediated calcium influx in cultured cerebral cortical, hippocampal and cerebellar neurons. Neurochem Res 2004;29:275–82 2004.

Qian J, Noebels JL. Topiramate alters excitatory synaptic transmission in mouse hippocampus. Epilepsy Res 2003;55:225–33.

Raffa RB, Rawls SM. Planaria: A Model for Drug Action and Abuse. Austin TX: Landes Bioscience; 2008.

Rawls SM, Gomez T, Raffa RB. An NMDA antagonist (LY 235959) attenuates abstinence-induced withdrawal of planarians following acute exposure to a cannabinoid agonist (WIN 55212-2). Pharmacol Biochem Behav 2007;86:499–504.

Rawls SM, Gomez T, Stagliano GW, Raffa RB. Measurement of glutamate and aspartate in *Planaria*. J Pharmacol Toxicol Methods 2006;53:291–5.

Russo E, Constanti A. Topiramate hyperpolarizes and modulates the slow post-stimulus AHP of rat olfactory cortical neurones in vitro. Br J Pharmacol 2004;141:285–301.

Shank RP, Maryanoff BE. Molecular pharmacodynamics clinical therapeutics and pharmacokinetics of topiramate. CNS Neurosci Ther 2008;14:120–42.

Shank RP, Doose DR, Streeter AJ, Bialer M. Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase. Epilepsy Res 2005;63:103–12.

Shank RP, Gardocki JF, Vaught JL, Davis CB, Schupsky JJ, Raffa RB, et al. Topiramate: preclinical evaluation of a structurally novel anticonvulsant. Epilepsia 1994;35: 450–60.

Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2000;41 Suppl 1:S3–9. Review.

Shank RP, McComsey DF, Smith-Swintosky VL, Maryanoff BE. Examination of two independent kinetic assays for determining the inhibition of carbonic anhydrases I and II: structure–activity comparison of sulfamates and sulfamides. Chem Biol Drug Design 2006;68:113–9.

Simeone TA, Wilcox KS, White HS. Subunit selectivity of topiramate modulation of heteromeric $GABA_A$. Neuropharmacology 2006;50:845–57.

Skradski S, White HS. Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia 2000;41(Suppl.1):S45–7.

Sun GC, Werkman TR, Battefeld A, Clare JJ, Wadman WJ. Carbamazepine and topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the Na_v 1.3 α-subunit. Epilepsia 2007;48:774–82.

Taverna S, Sancini G, Mantegazza M, Franceschetti S, Avanzini G. Inhibition of transient and persistent Na^+ current fractions by the new anticonvulsant topiramate. J Pharmacol Exp Ther 1999;288:960–8.

White HS, Brown SD, Skeen GA, Wolf HH, Twyman RE. The anticonvulsant topiramate displays a unique ability to potentiate GAB_A-evoked Cl^- currents. Epilepsia 1995;36 (Suppl. 3):S39-40.

White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH. Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. Epilepsy Res 1997;28:167–79.

White HS, Brown SD, Woodhead J, Skeen GA, Wolf HH. Topiramate modulates GABA-evoked currents in murine cortical neurons by a non-benzodiazepine mechanism. Epilepsia 2000;41(Suppl.1):S17-20.

Wu SP, Tsai JJ, Gean PW. Frequency-dependent inhibition of neuronal firing by topiramate in hippocampal slices. Brit J Pharmacol 1999;125:826–32.

Zhang X-L, Velumian AA, Jones OT, Carlen PL. Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 2000;41(Suppl.1): S52-60.

Ziemann U. Pharmacology of TMS. Suppl Clin Neurophysiol 2003;56:226–31.

Zona C, Ciotti MT, Avoli M. Topiramate attenuates voltage-gated sodium currents in rat cerebellar granule cells in culture. Neurosci Lett 1997;231:123–6.