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Pharmacodynamics of the glutamate receptor antagonists in the rat barrel cortex

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Abstract

© 2018 Vinokurova, Zakharov, Lebedeva, Burkhanova, Chernova, Lotfullina, Khazipov and Valeeva. Epipial application is one of the approaches for drug delivery into the cortex. However, passive diffusion of epipially applied drugs through the cortical depth may be slow, and different drug concentrations may be achieved at different rates across the cortical depth. Here, we explored the pharmacodynamics of the inhibitory effects of epipially applied ionotropic glutamate receptor antagonists CNQX and dAPV on sensory-evoked and spontaneous activity across layers of the cortical barrel column in urethane-anesthetized rats. The inhibitory effects of CNQX and dAPV were observed at concentrations that were an order higher than in slices in vitro, and they slowly developed from the cortical surface to depth after epipial application. The level of the inhibitory effects also followed the surface-to-depth gradient, with full inhibition of sensory evoked potentials (SEPs) in the supragranular layers and L4 and only partial inhibition in L5 and L6. During epipial CNQX and dAPV application, spontaneous activity and the late component of multiple unit activity (MUA) during sensory-evoked responses were suppressed faster than the short-latency MUA component. Despite complete suppression of SEPs in L4, sensory-evoked short-latency multiunit responses in L4 persisted, and they were suppressed by further addition of lidocaine suggesting that spikes in thalamocortical axons contribute ~20% to early multiunit responses. Epipial CNQX and dAPV also completely suppressed sensory-evoked very fast (~500 Hz) oscillations and spontaneous slow wave activity in L2/3 and L4. However, delta oscillations persisted in L5/6. Thus, CNQX and dAPV exert inhibitory actions on cortical activity during epipial application at much higher concentrations than in vitro, and the pharmacodynamics of their inhibitory effects is characterized by the surface-to-depth gradients in the rate of development and the level of inhibition of sensory-evoked and spontaneous cortical activity.

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Keywords

Barrel cortex, Drug delivery, Epipial application, Fast oscillations, Glutamate receptor antagonists, Sensory-evoked potential, Slow wave activity

References

[1] Andreasen, M., Lambert, J. D. C., and Jensen, M. S. (1989). Effects of new non-N-methyl-D-aspartate antagonists on synaptic transmission in the in vitro rat hippocampus. J. Physiol. 414, 317-336. doi: 10.1113/jphysiol.1989.sp017690

[2] Barth, D. S. (2003). Submillisecond synchronization of fast electrical oscillations in neocortex. J. Neurosci. 23, 2502-2510. doi: 10.1523/JNEUROSCI.23-06-02502.2003

[3] Bartho, P., Hirase, H., Monconduit, L., Zugaro, M., Harris, K. D., and Buzsaki, G. (2004). Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. J. Neurophysiol. 92, 600-608. doi: 10.1152/jn.01170.2003

[4] Bondareff, W., and Narotzky, R. (1972). Age changes in the neuronal microenvironment. Science 176, 1135-1136. doi: 10.1126/science.176.4039.1135

[5] Bondareff, W., and Pysh, J. J. (1968). Distribution of the extracellular space during postnatal maturation of rat cerebral cortex. Anat. Rec. 160, 773-780. doi: 10.1002/ar.1091600412

[6] Brecht, M. (2007). Barrel cortex and whisker-mediated behaviors. Curr. Opin. Neurobiol. 17, 408-416. doi: 10.1016/j.conb.2007.07.008

[7] Bruno, R. M., and Sakmann, B. (2006). Cortex is driven by weak but synchronously active thalamocortical synapses. Science 312, 1622-1627. doi: 10.1126/science.1124593

[8] Bureau, I., von Saint, P. F., and Svoboda, K. (2006). Interdigitated paralemniscal and lemniscal pathways in the mouse barrel cortex. PLoS Biol. 4:e382. doi: 10.1371/journal.pbio.0040382

[9] Buzsaki, G. (2006). Rhythms of the Brain. Oxford: Oxford University Press. doi: 10.1093/acprof:oso/9780195301069.001.0001

[10] Buzsaki, G., Anastassiou, C. A., and Koch, C. (2012). The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes. Nat. Rev. Neurosci. 13, 407-420. doi: 10.1038/nrn3241

[11] Castro-Alamancos, M. A., and Oldford, E. (2002). Cortical sensory suppression during arousal is due to the activity-dependent depression of thalamocortical synapses. J. Physiol. 541, 319-331. doi: 10.1113/jphysiol.2002.016857

[12] Chmielowska, J., Carvell, G. E., and Simons, D. J. (1989). Spatial organization of thalamocortical and corticothalamic projection systems in the rat SmI barrel cortex. J. Comp. Neurol. 285, 325-338. doi: 10.1002/cne.902850304

[13] Constantinople, M. C., and Bruno, R. M. (2013). Deep cortical layers are activated directly by thalamus. Science 340, 1591-1594. doi: 10.1126/science.1236425

[14] Conti, F., and Minelli, A. (1994). Glutamate immunoreactivity in rat cerebral cortex is reversibly abolished by 6-diazo-5-oxo-L-norleucine (DON), an inhibitor of phosphate-activated glutaminase. J. Histochem. Cytochem. 42, 717-726. doi: 10.1177/42.6.7910617

[15] Crocker-Buque, A., Brown, S. M., Kind, P. C., Isaac, J. T., and Daw, M. I. (2015). Experience-dependent, layer-specific development of divergent thalamocortical connectivity. Cereb. Cortex 25, 2255-2266. doi: 10.1093/cercor/bhu031

[16] Davies, J., Francis, A. A., Jones, A. W., and Watkins, J. C. (1981). 2-Amino-5-phosphonovalerate (2APV), a potent and selective antagonist of amino acid-induced and synaptic excitation. Neurosci. Lett. 21, 77-81. doi: 10.1016/0304-3940(81)90061-6

[17] Di, S., Baumgartner, C., and Barth, D. S. (1990). Laminar analysis of extracellular field potentials in rat vibrissa/barrel cortex. J. Neurophysiol. 63, 832-840. doi: 10.1152/jn.1990.63.4.832

[18] Douglas, R. J., and Martin, K. A. (2004). Neuronal circuits of the neocortex. Annu. Rev. Neurosci. 27, 419-451. doi: 10.1146/annurev.neuro.27.070203.144152

[19] Feldman, D. E., Nicoll, R. A., Malenka, R. C., and Isaac, J. T. (1998). Long-term depression at thalamocortical synapses in developing rat somatosensory cortex. Neuron 21, 347-357. doi: 10.1016/S0896-6273(00)80544-9

[20] Feldmeyer, D. (2012). Excitatory neuronal connectivity in the barrel cortex. Front. Neuroanat. 6:24. doi: 10.3389/fnana.2012.00024

[21] Feldmeyer, D., Brecht, M., Helmchen, F., Petersen, C. C., Poulet, J. F., Staiger, J. F., et al. (2013). Barrel cortex function. Prog. Neurobiol. 103, 3-27. doi: 10.1016/j.pneurobio.2012.11.002

[22] Groothuis, D. R., Vavra, M. W., Schlageter, K. E., Kang, E. W., Itskovich, A. C., and Hertzler, S. (2007). Efflux of drugs and solutes from brain: the interactive roles of diffusional transcapillary transport, bulk flow and capillary transporters. J. Cereb. Blood Flow Metab. 27, 43-56. doi: 10.1038/sj.jcbfm.9600315

[23] Hablitz, J. J., and Sutor, B. (1990). Excitatory postsynaptic potentials in rat neocortical neurons in vitro. III. Effects of a quinoxalinedione non-NMDA receptor antagonist. J. Neurophysiol. 64, 1282-1290. doi: 10.1152/jn.1990.64.4.1282

[24] Hagen, E., Fossum, J. C., Pettersen, K. H., Alonso, J. M., Swadlow, H. A., and Einevoll, G. T. (2017). Focal local field potential signature of the single-axon monosynaptic thalamocortical connection. J. Neurosci. 37, 5123-5143. doi: 10.1523/JNEUROSCI.2715-16.2017

[25] Henze, D. A., Borhegyi, Z., Csicsvari, J., Mamiya, A., Harris, K. D., and Buzsaki, G. (2000). Intracellular features predicted by extracellular recordings in the hippocampus in vivo. J. Neurophysiol. 84, 390-400. doi: 10.1152/jn.2000.84.1.390

[26] Homola, A., Zoremba, N., Slais, K., Kuhlen, R., and Sykova, E. (2006). Changes in diffusion parameters, energy-related metabolites and glutamate in the rat cortex after transient hypoxia/ischemia. Neurosci. Lett. 404, 137-142. doi: 10.1016/j.neulet.2006.05.028

[27] Honore, T., Davies, S. N., Drejer, J., Fletcher, E. J., Jacobson, P., Lodge, D., et al. (1988). Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. Science 241, 701-703. doi: 10.1126/science.2899909

[28] Ikeda, H., Leyba, L., Bartolo, A., Wang, Y., and Okada, Y. C. (2002). Synchronized spikes of thalamocortical axonal terminals and cortical neurons are detectable outside the pig brain with MEG. J. Neurophysiol. 87, 626-630. doi: 10.1152/jn.00332.2001

[29] Johnston, D., and Brown, T. H. (1981). Giant synaptic potential hypothesis for epileptiform activity. Science 211, 294-297. doi: 10.1126/science.7444469

[30] Jones, M. S., and Barth, D. S. (1999). Spatiotemporal organization of fast (>200 Hz) electrical oscillations in rat Vibrissa/Barrel cortex. J. Neurophysiol. 82, 1599-1609. doi: 10.1152/jn.1999.82.3.1599

[31] Jones, M. S., MacDonald, K. D., Choi, B., Dudek, F. E., and Barth, D. S. (2000). Intracellular correlates of fast (>200 Hz) electrical oscillations in rat somatosensory cortex. J. Neurophysiol. 84, 1505-1518. doi: 10.1152/jn.2000.84.3.1505

[32] Kandel, A., and Buzsaki, G. (1997). Cellular-synaptic generation of sleep spindles, spike-and-wave discharges, and evoked thalamocortical responses in the neocortex of the rat. J. Neurosci. 17, 6783-6797. doi: 10.1523/JNEUROSCI.17-17-06783.1997

[33] Keep, R. F., and Jones, H. C. (1990). Cortical microvessels during brain development: a morphometric study in the rat. Microvasc. Res. 40, 412-426. doi: 10.1016/0026-2862(90)90036-Q

[34] Khazipov, R., and Holmes, G. L. (2003). Synchronization of kainate-induced epileptic activity via GABAergic inhibition in the superfused rat hippocampus in vivo. J. Neurosci. 23, 5337-5341. doi: 10.1523/JNEUROSCI.23-12-05337.2003

[35] Khazipov, R., Zaynutdinova, D., Ogievetsky, E., Valeeva, G., Mitrukhina, O., Manent, J. B., et al. (2015). Atlas of the postnatal rat brain in stereotaxic coordinates. Front. Neuroanat. 9:161. doi: 10.3389/fnana.2015.00161

[36] Kilb, W., Dierkes, P. W., Sykova, E., Vargova, L., and Luhmann, H. J. (2006). Hypoosmolar conditions reduce extracellular volume fraction and enhance epileptiform activity in the CA3 region of the immature rat hippocampus. J. Neurosci. Res. 84, 119-129. doi: 10.1002/jnr.20871

[37] Kohling, R., Lehmenkukhler, A., Nicholson, C., and Speckmann, E. J. (1993). Superfusion of verapamil on the cerebral cortex does not suppress epileptic discharges due to restricted diffusion (rats, in vivo). Brain Res. 626, 149-155. doi: 10.1016/0006-8993(93)90574-7

[38] Laurent, A., Goaillard, J. M., Cases, O., Lebrand, C., Gaspar, P., and Ropert, N. (2002). Activity-dependent presynaptic effect of serotonin 1B receptors on the somatosensory thalamocortical transmission in neonatal mice. J. Neurosci. 22, 886-900. doi: 10.1523/JNEUROSCI.22-03-00886.2002

[39] Lehmenkuhler, A., Sykova, E., Svoboda, J., Zilles, K., and Nicholson, C. (1993). Extracellular space parameters in the rat neocortex and subcortical white matter during postnatal development determined by diffusion analysis. Neuroscience 55, 339-351. doi: 10.1016/0306-4522(93)90503-8

[40] Llano, I., Marty, A., Armstrong, C. M., and Konnerth, A. (1991). Synaptic-and agonist-induced excitatory currents of Purkinje cells in rat cerebellar slices. J. Physiol. 434, 183-213. doi: 10.1113/jphysiol.1991.sp018465

[41] Long, S. K., Smith, D. A., Siarey, R. J., and Evans, R. H. (1990). Effect of 6-cyano-2, 3-dihydroxy-7-ni-ro-quinoxaline (CNQX) on dorsal root-, NMDA-, kainate-and quisqualate-mediated depolarization of rat motoneurones in vitro. Br. J. Pharmacol. 100, 850-854. doi: 10.1111/j.1476-5381.1990.tb14103.x

[42] Lu, S. M., and Lin, R. C. (1993). Thalamic afferents of the rat barrel cortex: a light-and electron-microscopic study using Phaseolus vulgaris leucoagglutinin as an anterograde tracer. Somatosens. Mot. Res. 10, 1-16. doi: 10.3109/08990229309028819

[43] Mazel, T., Richter, F., Vargova, L., and Sykova, E. (2002). Changes in extracellular space volume and geometry induced by cortical spreading depression in immature and adult rats. Physiol. Res. 51(Suppl. 1), S85-S93

[44] Mazel, T., Simonova, Z., and Sykova, E. (1998). Diffusion heterogeneity and anisotropy in rat hippocampus. Neuroreport 9, 1299-1304. doi: 10.1097/00001756-199805110-00008

[45] Meyer, H. S., Wimmer, V. C., Oberlaender, M., de Kock, C. P., Sakmann, B., and Helmstaedter, M. (2010). Number and laminar distribution of neurons in a thalamocortical projection column of rat vibrissal cortex. Cereb. Cortex 20, 2277-2286. doi: 10.1093/cercor/bhq067

[46] Minlebaev, M., Ben Ari, Y., and Khazipov, R. (2009). NMDA receptors pattern early activity in the developing barrel cortex in vivo. Cereb. Cortex 19, 688-696. doi: 10.1093/cercor/bhn115

[47] Minlebaev, M., Ben-Ari, Y., and Khazipov, R. (2007). Network mechanisms of spindle-burst oscillations in the neonatal rat barrel cortex in vivo. J. Neurophysiol. 97, 692-700. doi: 10.1152/jn.00759.2006

[48] Minlebaev, M., Colonnese, M., Tsintsadze, T., Sirota, A., and Khazipov, R. (2011). Early gamma oscillations synchronize developing thalamus and cortex. Science 334, 226-229. doi: 10.1126/science.1210574

[49] Neuman, R. S., Ben-Ari, Y., Gho, M., and Cherubini, E. (1988). Blockade of excitatory synaptic transmission by 6-cyano-7-nitroquinoxaline-2, 3-dione (CNQX) in the hippocampus in vitro. Neurosci. Lett. 92, 64-68. doi: 10.1016/0304-3940(88)90743-4

[50] Nicholson, C., and Phillips, J. M. (1981). Ion diffusion modified by tortuosity and volume fraction in the extracellular microenvironment of the rat cerebellum. J. Physiol. 321, 225-257. doi: 10.1113/jphysiol.1981.sp013981

[51] Oberlaender, M., de Kock, C. P., Bruno, R. M., Ramirez, A., Meyer, H. S., Dercksen, V. J., et al. (2012). Cell type-specific three-dimensional structure of thalamocortical circuits in a column of rat vibrissal cortex. Cereb. Cortex 22, 2375-2391. doi: 10.1093/cercor/bhr317

[52] Ohata, K., and Marmarou, A. (1992). Clearance of brain edema and macromolecules through the cortical extracellular space. J. Neurosurg. 77, 387-396. doi: 10.3171/jns.1992.77.3.0387

[53] Paxinos, G., and Watson, C. (2007). The Rat Brain in Stereotaxic Coordinates, 6th Edn. San Diego, CA: Academic Press

[54] Petersen, C. C. (2007). The functional organization of the barrel cortex. Neuron 56, 339-355. doi: 10.1016/j.neuron.2007.09.017

[55] Pockberger, H., Rappelsberger, P., and Petsche, H. (1984). Penicillin-induced epileptic phenomena in the rabbit's neocortex I. The development of interictal spikes after epicortical application of penicillin. Brain Res. 309, 247-260. doi: 10.1016/0006-8993(84)90591-2

[56] Reum, T., Olshausen, F., Mazel, T., Vorisek, I., Morgenstern, R., and Sykova, E. (2002). Diffusion parameters in the striatum of rats with 6-hydroxydopamine-induced lesions and with fetal mesencephalic grafts. Neurosci. Res. 70, 680-693. doi: 10.1002/jnr.10332

[57] Reyes-Puerta, V., Sun, J. J., Kim, S., and Luhmann, H. J. (2015). Laminar and columnar structure of sensory-evoked multineuronal spike sequences in adult rat barrel cortex in vivo. Cereb. Cortex 25, 2001-2021. doi: 10.1093/cercor/bhu007

[58] Risser, L., Plouraboue, F., Cloetens, P., and Fonta, C. (2009). 3D-investigation shows that angiogenesis in primate cerebral cortex mainly occurs at capillary level. Int. J. Dev. Neurosci. 27, 185-196. doi: 10.1016/j.ijdevneu.2008.10.006

[59] Roy, N. C., Bessaih, T., and Contreras, D. (2011). Comprehensive mapping of whisker-evoked responses reveals broad, sharply tuned thalamocortical input to layer 4 of barrel cortex. J. Neurophysiol. 105, 2421-2437. doi: 10.1152/jn.00939.2010

[60] Sakata, S., and Harris, K. D. (2009). Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. Neuron 64, 404-418. doi: 10.1016/j.neuron.2009.09.020

[61] Sanchez-Vives, M. V., and McCormick, D. A. (2000). Cellular and network mechanisms of rhythmic recurrent activity in neocortex. Nat. Neurosci. 3, 1027-1034. doi: 10.1038/79848

[62] Silva, L. R., Amitai, Y., and Connors, B. W. (1991). Intrinsic oscillations of neocortex generated by layer five pyramidal neurons. Science 251, 432-435. doi: 10.1126/science.1824881

[63] Simonova, Z., Svoboda, J., Orkand, P., Bernard, C. C. A., Lassmann, H., and Sykova, E. (1996). Changes of extracellular space volume and tortuosity in the spinal cord of Lewis rats with experimental autoimmune encephalomyelitis. Physiol. Res. 45, 11-22

[64] Slais, K., Vorisek, I., Zoremba, N., Homola, A., Dmytrenko, L., and Sykova, E. (2008). Brain metabolism and diffusion in the rat cerebral cortex during pilocarpine-induced status epilepticus. Exp. Neurol. 209, 145-154. doi: 10.1016/j.expneurol.2007.09.008

[65] Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. J. Neurophysiol. 86, 1-39. doi: 10.1152/jn.2001.86.1.1

[66] Svoboda, J., and Sykova, E. (1991). Extracellular space volume changes in the rat spinal cord produced by nerve stimulation and peripheral injury. Brain Res. 560, 216-224. doi: 10.1016/0006-8993(91)91235-S

[67] Swadlow, H. A., and Gusev, A. G. (2002). Receptive-field construction in cortical inhibitory interneurons. Nat. Neurosci. 5, 403-404. doi: 10.1038/nn847

[68] Swadlow, H. A., Gusev, A. G., and Bezdudnaya, T. (2002). Activation of a cortical column by a thalamocortical impulse. J. Neurosci. 22, 7766-7773. doi: 10.1523/JNEUROSCI.22-17-07766.2002

[69] Sykova, E., Mazel, T., Hasenohrl, R. U., Harvey, A. R., Simonova, Z., Mulders, W., et al. (2002). Learning deficits in aged rats related to decrease in extracellular volume and loss of diffusion anisotropy in hippocampus. Hippocampus 12, 269-279. doi: 10.1002/hipo.1101

[70] Sykova, E., Mazel, T., and Simonova, Z. (1998). Diffusion constraints and neuron-glia interaction during aging. Exp. Gerontol. 33, 837-851. doi: 10.1016/S0531-5565(98)00038-2

[71] Sykova, E., and Nicholson, C. (2008). Diffusion in brain extracellular space. Physiol. Rev. 88, 1277-1340. doi: 10.1152/physrev.00027.2007

[72] Sykova, E., Svoboda, J., Polak, J., and Vatal, A. (1994). Extracellular volume fraction and diffusion characteristics during progressive ischemia and terminal anoxia in the spinal cord of the rat. Cereb. Blood Flow Metab. 14, 301-311. doi: 10.1038/jcbfm.1994.37

[73] Sykova, E., Vorisek, I., Mazel, T., Antonova, T., and Schachner, M. (2005). Reduced extracellular space in the brain of tenascin-R-and HNK-1-sulphotransferase deficient mice. Eur. J. Neurosci. 22, 1873-1880. doi: 10.1111/j.1460-9568.2005.04375.x

[74] Timofeev, I., Grenier, F., Bazhenov, M., Sejnowski, T. J., and Steriade, M. (2000). Origin of slow cortical oscillations in deafferented cortical slabs. Cereb. Cortex 10, 1185-1199. doi: 10.1093/cercor/10.12.1185

[75] Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., et al. (2010). Glutamate receptor ion channels: structure, regulation, and function. Pharmacol. Rev. 62, 405-496. doi: 10.1124/pr.109.002451

[76] Vargova, L., Homola, A., Amecnik, J., Tichy, M., Benes, V., and Sykova, E. (2003). Diffusion parameters of the extracellular space in human gliomas. Glia 42, 47-88. doi: 10.1002/glia.10204

[77] Vorisek, I., Hajek, M., Tintera, J., Nicolay, K., and Sykova, E. (2002). Water ADC, extracellular space volume, and tortuosity in the rat cortex after traumatic injury. Magn. Res. Med. 48, 994-1003. doi: 10.1002/mrm.10305

[78] Vorisek, I., and Sykova, E. (1997a). Evolution of anisotropic diffusion in the developing rat corpus callosum. J. Neurophysiol. 78, 912-919

[79] Vorisek, I., and Sykova, E. (1997b). Ischemia-induced changes in the extracellular space diffusion parameters, K+, and pH in the developing rat cortex and corpus callosum. J. Cereb. Blood Flow Metab. 17, 191-203

[80] Yang, J. W., An, S., Sun, J. J., Reyes-Puerta, V., Kindler, J., Berger, T., et al. (2013). Thalamic network oscillations synchronize ontogenetic columns in the newborn rat barrel cortex. Cereb. Cortex 23, 1299-1316. doi: 10.1093/cercor/bhs103

[81] Yu, B. P., Yu, C. C., and Robertson, R. T. (1994). Patterns of capillaries in developing cerebral and cerebellar cortices of rats. Acta Anat. 149, 128-133. doi: 10.1159/000147567