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Inhibition of Metaphit-Induced Audiogenic Seizures by APV in Rats

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Summary

The influence of APV ((±)-2-amino-5-phosphonovaleric acid) on EEG activity and behavior was studied on a model of epilepsy induced by intraperitoneal administration of metaphit (1-(1-(3-isothiocyanatophenyl)-cyclohexyl)-piperidine). Male Wistar rats received an injection of metaphit (10 mg/kg) and were subjected to intense audio stimulation (100±3 dB, 60 s) at hourly intervals during the experiment. The seizures were classified according to a four point scale ranging from 0 (no seizure) to 3 (tonic convulsions). In our report we studied the time course which revealed the maximum incidence and severity of seizures 7-12 h after the injection (10 out of 12 rats, with severity of 2.25±0.32). APV (0.05, 0.1, 0.2 and 0.3 μmol) was injected intracerebroventricularly at the time of fully developed convulsions. APV inhibited seizures in a dose-dependent manner. The minimum dose, which completely blocked seizures in all animals, was 0.3 μmol, while ED_{50} were 0.11, 0.10 and 0.07 μmol against running, clonus and tonus, respectively. In contrast to behavioral inhibition of convulsions, metaphit-provoked epileptiform activity was not abolished by APV, and represented a prerequisite for the reappearance of behavioral seizures. It is suggested that APV is rather an anticonvulsant than an antiepileptic agent in this model of epilepsy.

Key words
Rat • Metaphit • Audiogenic seizures • APV • EEG

Introduction

Metaphit (1-(1-(3-isothiocyanatophenyl)-cyclohexyl)-piperidine) is a derivative of phencyclidine (PCP) containing an isothiocyanate group on the meta position of the aromatic ring. Metaphit is known to interact with the PCP recognition site of NMDA (N-methyl-D-aspartate) receptor complex (Rafferty *et al.* 1985), dopamine uptake site (Berger *et al.* 1986) and with voltage-dependent sodium channels (Reith *et al.* 1991). Metaphit shares many characteristics of its parent compound and, unexpectedly, is capable of turning normal rodents into animals susceptible to audiogenic seizures (AGS) (Debler *et al.* 1989, Šušic *et al.* 1991). In contrast to metaphit, PCP blocks audiogenic seizures very efficiently (Debler *et al.* 1989). Metaphit lowers the threshold for other epileptogenic stimuli, e.g. picrotoxin, NMDA and kindling, which potentiate metaphit-induced AGS (Debler *et al.* 1993, Chen *et al.* 1994). Metaphit-induced audiogenic seizures could be blocked by general anticonvulsants as well as by competitive and noncompetitive NMDA receptor antagonists (Debler *et al.* 1989, 1993, Zivanovic *et al.* 1997a).

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APV ((±)-2-amino-5-phosphonovaleric acid), a competitive antagonist of NMDA receptors, is capable of blocking epileptic manifestations when injected by the systemic, intracerebroventricular or intracerebral route. APV significantly elevated the threshold for maximal electroconvulsions in mice (Czuczwar *et al.* 1984), blocked audiogenic seizures in DBA/2 mice (Meldrum *et al.* 1983a), inhibited chemically-induced seizures in mice and rats (Loeb *et al.* 1990, Meldrum *et al.* 1983a) and suppressed photically induced myoclonus in *Papio papio* baboons (Meldrum *et al.* 1983b). APV retarded clinical seizure development of amygdala-kindled rats, and had strong anticonvulsant effects on previously kindled animals (Cain *et al.* 1988). In *in vitro* electrophysiological study of human temporal lobe epilepsy refractory to conventional anticonvulsant therapy APV was capable of reducing and/or blocking burst of action potentials evoked by extracellular stimulation (Avoli and Olivier 1987).

The aim of this study was to assess anticonvulsant and/or antiepileptic potency of APV against metaphit-induced audiogenic seizures in rats. Preliminary report of these data has appeared in abstract form (Živanović *et al.* 1997b).

Method

Male Wistar albino rats (Military Medical Academy Breeding Laboratory, Belgrade, Yugoslavia), weighing 180-200 g, were used in experiments. The animals were kept on a 12-h light/dark schedule (light on at 09:00 h) in a quiet room, at a temperature of 23-24 °C and 50 % humidity. Animals were housed individually in transparent plastic cages (55×35×30 cm) with food (Purina rat chow) and water *ad libitum*. None of the animals, screened for audiogenic susceptibility, exhibited seizure activity.

Rats were anesthetized intraperitoneally (i.p.) with sodium pentobarbital (40 mg/kg) and placed in a stereotaxic apparatus. A stainless-steel guide cannula was inserted unilaterally into the lateral ventricle (coordinates from bregma: P=1.3, L=2.0, 4.5 mm depth from skull surface) according to the atlas of Paxinos and Watson (1982), and three gold-plated screws (tip diameter 0.6 mm) were implanted over the frontal, parietal and occipital cortices for electroencephalographic recordings.

The experiments were performed at least one week after surgery. The subjects were randomly assigned to the following treatment groups: saline (i.p.) (n=5), metaphit (i.p.) (n=12), metaphit (i.p.) + saline (i.c.v.) (n=7), metaphit (i.p.) + APV (i.c.v.) (n=33), and APV (i.c.v.) (n=8).

Metaphit, dissolved in sterile saline, was injected i.p. in a dose of 10 mg/kg. All metaphit injections were given between 09:00 and 09:30 h in a volume 0.1 ml. APV was administered intracerebroventricularly by a 10 µl Hamilton syringe through a cannula after the 8th audiogenic testing session. The doses of APV were: 0.05 (n=7), 0.1 (n=8), 0.2 (n=9), and 0.3 µmol (n=9), all added to 5 µl of physiological saline. The rate of injection was 1 µl/5 s, and the needle remained *in situ* for another 30 s to prevent backflow of the solution.

Auditory stimulation was applied for 60 s using an electric bell (on the top of the cage) generating 100±3 dB at the level of the animal's head. The first sound stimulus was administered 1 h after the metaphit injection and repeated at 1-h intervals to individual rats from all groups. Seizure related activity was classified according to the descriptive scale: 0 – no response, 1 – wild running only, 2 – wild running followed by clonic seizures, and 3 – wild running, clonic and tonic convulsions. Electroencephalographic (EEG) activity was recorded on an 8-channel RIZ EEG apparatus for one hour before the experiments (baseline) and up to 33 h after the injections. EEG tracings were inspected visually. At the end of the experiments, before sacrificing the animals, 5 µl of blue ink were injected through the cannula. The cannulas were found to be placed correctly in the lateral ventricle in all animals.

ED_{50} was calculated according to Litchfield and Wilcoxon (1949). Statistical comparisons between metaphit and metaphit + APV groups were carried out by means of the Kruskal-Wallis one-way ANOVA, Mann-Whitney U test, one-way ANOVA, and Fisher's exact probability test. Comparisons within individual groups were done according to Friedman's two-way ANOVA and the Wilcoxon test.

The drugs used in this study were metaphit (methanesulfonate salt) and APV ((±)-2-amino-5-phosphonovaleric acid) obtained from ICN Biomedicals Inc. (Costa Mesa, CA, USA).

Results

Saline injections changed neither spontaneous behavior, nor EEG activity. In response to sound stimulation, control animals showed short-lasting EEG desynchronization and an orienting reaction.

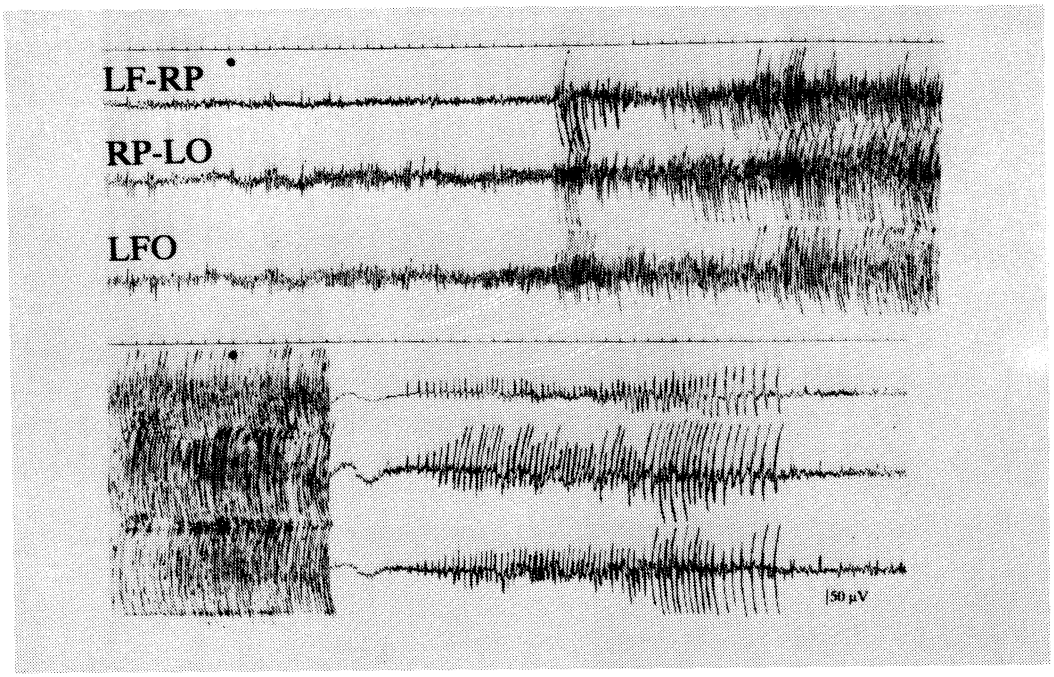

Fig. 1. *EEG tracing of complete motor seizure response (grade 3) in metaphit-treated rat (10 mg/kg, i.p.) during sound stimulation (100±3 dB, 60 s). Spots indicate onset and termination of audio stimulation. Note profound postictal depression. Time calibration 1 s. LF-RP – left fronto-right parietal, RP-LO right parietal-left occipital, LFO – left fronto-occipital cortex.*

Table 1. Dose-dependent blockade of metaphit-induced audiogenic seizures by APV

Group	APV (μmol)	n	Mean seizure grade 8 h	9 h	10 h	11 h	12 h	Number of rats convulsing 8 h	9 h	10 h	11 h	12 h
Metaphit		12	2.00	1.91	2.25	1.91	2.00	9	9	10	9	9
Metaphit+APV	0.05	7	2.28	1.57	2.00	1.85	1.85	6	5	5	5	5
	0.1	8	2.25	1.12$^{\#}$	1.75	1.75	2.12	7	4	6	6	6
	0.2	9	2.00	0.66*$^{\#}$	0.88*$^{\#}$	1.44	1.44	7	2*	4	5	5
	0.3	9	2.22	0.00**$^{\#}$	0.11**$^{\#}$	0.22**$^{\#}$	0.33**$^{\#}$	7	0**	1**	2*	2*
Metaphit+S		7	2.28	2.42	2.14	2.14	1.71	6	6	6	6	5

*Metaphit-treated rats (10 mg/kg, i.p.) were exposed to sound stimulation (100±3 dB, 60 s) at 1-h intervals after the injection. After the 8th audiogenic testing APV or saline were administered i.c.v. S – saline, n – number of animals in group. Comparison of mean seizure grade to the value in the 8th hour for the same group (Wilcoxon test, #p<0.05). Comparison of mean seizure grades between metaphit and metaphit+APV groups (Kruskal-Wallis one-way ANOVA and Mann-Whitney U test, *p<0.05, **p<0.01). Comparison of the number of rats convulsing between metaphit and metaphit+APV groups (Fisher's exact probability test, *p<0.05, **p<0.01).*

EEG tracings of metaphit-treated rats (10 mg/kg, i.p.) showed that the epileptiform activity was starting approximately 30 min after the injection. Isolated spikes, polyspikes and spike-wave complexes of high amplitude reappeared at progressively shorter intervals and culminated in electroencephalographic

seizures which were not followed by behavioral manifestations. During these EEG seizures the animals were quiet without any behavioral signs of seizure activity. Behavioral seizures were elicited by audio stimulation. After a latency from the onset of sound, the rats displayed wild running bouts that quickly evolved into generalized clonic and then tonic convulsions. The most severe seizures (grade 3) persisting after the stimulation had been discontinued and were followed by behavioral and EEG depression (Fig. 1). The incidence and severity of convulsions increased with time, reached a peak 7-12 h after metaphit administration (10 out of 12 animals, 2.25±0.32) and then gradually decreased until 31 h post-injection, when no animal displayed any audiogenic seizure symptoms. There were no significant differences in the period from the 8th to 12th hour in the mean seizure grades (Friedman two-way ANOVA, χ^2=0.88, dF=4, p>0.05) (Table 1), latency to convulsions (Friedman two-way ANOVA, χ^2=2.12, dF=4, p>0.05) (Table 2) and duration of wild running, clonic and tonic seizures (Friedman two-way ANOVA, running: χ^2=2.92, dF=4, p>0.05; clonus: χ^2=1.77, dF=4, p>0.05; tonus: χ^2=3.76, dF=4, p>0.05) (Fig. 2). Rats injected i.c.v. with 5 μl of saline after the 8th testing also did not show any difference in these parameters.

In order to investigate the anticonvulsant and antiepileptic potency of APV on fully developed seizures, APV was injected at the peak of metaphit convulsant action (after the 8th testing). The incidence and severity of seizures was progressively increasing in all experimental groups until the application of APV. APV blocked metaphit-induced AGS in a dose-dependent manner (Table 1). The lower doses (0.05 and 0.1 μmol) did not reduce the incidence and severity of convulsions significantly. The injection of 0.2 μmol of APV significantly decreased seizure severity scores for two hours, and five out of seven animals showed complete abolition of seizures. Following the administration of 0.3 μmol of APV complete suppression of seizures was observed for one hour, after which seizures reappeared, but significant difference lasted for 4 h (Table 1). A comparison within individual groups with the value in the 8th hour revealed a difference in mean seizure grade after 0.1 μmol in the 9th hour, after 0.2 μmol in the 9th and the 10th hour, and after 0.3 μmol during four post-injection hours (Wilcoxon test, p<0.05). The mean latency of seizures in control and experimental groups and within individual groups differed significantly only after 0.05 μmol of APV (one-way ANOVA, p<0.05; Wilcoxon test, p<0.05) (Table 2). ED_{50} with 95 % confidence limits in parentheses against running, clonic and tonic symptoms are 0.1197 (0.0508-0.2014), 0.1037 (0.0532-0.1560) and 0.0712 (0.0103-0.1791), respectively (Litchfield and Wilcoxon 1949). The duration of wild running, clonic and tonic convulsions are presented in Figure 2.

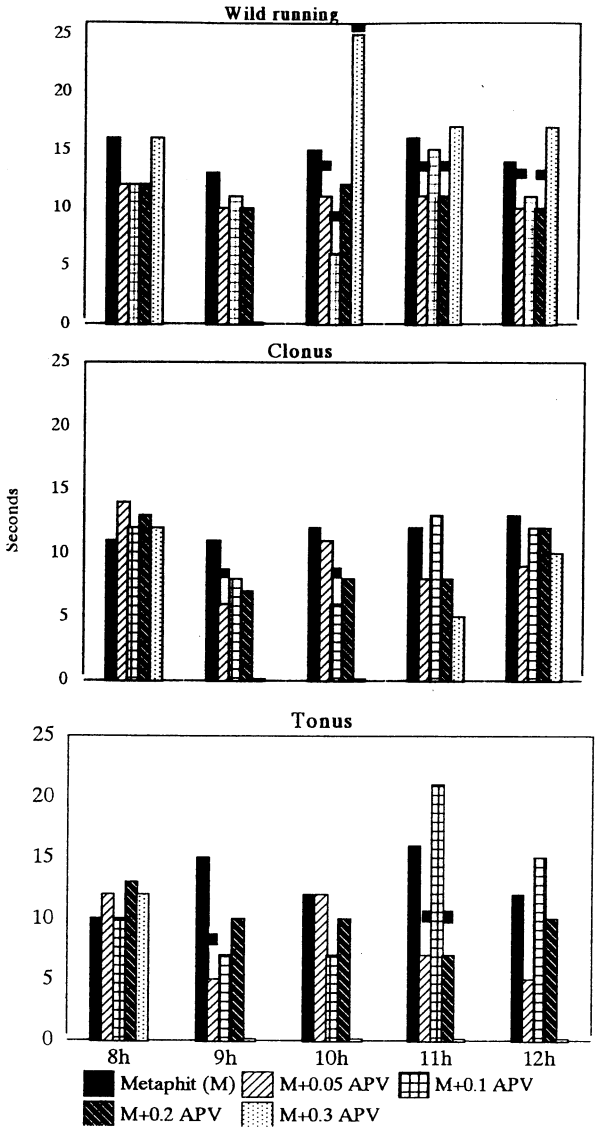

Fig. 2. *Durations of principal phases of audiogenic seizure response. Comparison between metaphit group and experimental groups (one-way ANOVA, full square indicates p<0.05).*

The dose of 0.3 μmol, which completely suppressed behavioral seizures, was ineffective in blocking paroxysmal discharges elicited by metaphit. After APV administration, spikes and spontaneous electrographic seizures were still present in the EEG.

Table 2. Latency to metaphit-induced audiogenic seizures

Group	APV (μmol)	n	Latency (s) 8 h	9 h	10 h	11 h	12 h
Metaphit		12	26±7	28±11	30±12	30±11	33±10
Metaphit + APV	0.05	7	30±2	44±11*	36±83$^{\#}$	36±8$^{\#}$	36±8$^{\#}$
	0.1	8	28±19	23±15	30±10	26±14	25±11
	0.2	9	32±15	38±11	31±8	36±12	40±10
	0.3	9	29±10	–	35	35±7	35±7
Metaphit + S		7	25±12	25±12	29±12	32±16	30±12

*Latency - time from the onset of sound stimulation to the onset of running. Values are means ± S.D. S – saline, n – number of animals. APV and saline were injected i.c.v. after the 8th testing to metaphit (10 mg/kg)-treated rats. Significant difference in the latency onset between metaphit and metaphit + APV groups (one-way ANOVA, *p<0.05). Comparison to the value in the 8th hour within group (Wilcoxon test, $^{\#}$p<0.05).*

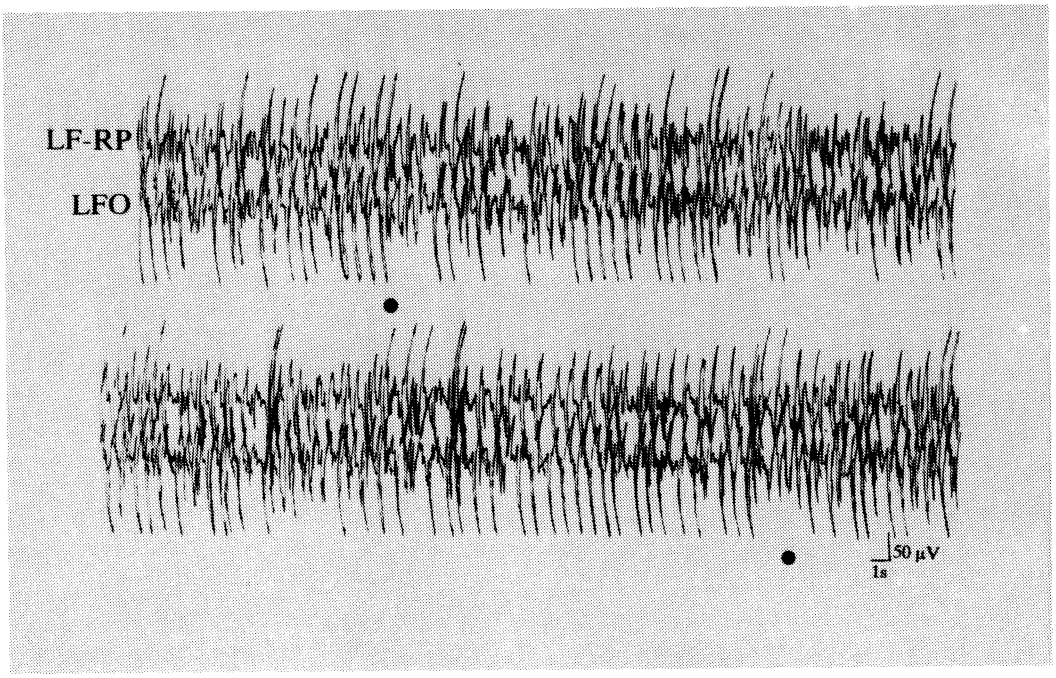

Fig. 3. *EEG record of audiogenic stimulation (100±3 dB, 60 s) applied 10 min after the injection of 0.3 μmol of APV. Spots denote onset and offset of sound stimulus. Note high amplitude low-frequency spikes and waves, and absence of any change in the record during the stimulation. Abbreviation as in Figure 1.*

Anticonvulsant action of APV was associated with the side effects which appeared 5-10 min after its administration and consisted of slight ataxia, decreased muscle tone, reduction in locomotor activity and occasional stumbling, without a loss of the righting reflex. Visual observation suggested that the severity and duration of ataxia was dose-related. The adverse behavioral effects after 0.3 μmol of APV lasted about 50 min.

Eight rats received an i.c.v. injection of 0.3 μmol of APV only. Soon after the injection, short-lasting bursts of high amplitude spikes appeared in the

EEG. In three animals a gradual increase in spiking activity was observed during 20 min which was then followed by a gradual decrease in the next 10-15 min to the pre-injection pattern. These continuous paroxysmal EEG patterns were not interrupted by acoustic or cutaneous stimulation (Fig. 3). Locomotor stimulation, stereotyped behavior and ataxia coincided with the appearance of low-frequency high-amplitude spikes and sharp waves in the EEG. APV occasionally elicited stumbling, but the righting reflex was not lost. Behavioral effects lasted approximately 10 min longer than the EEG changes.

Discussion

The anticonvulsant effect of APV against sound-induced seizures in metaphit-treated rats is in general agreement with the results of previous studies in rodent models (Meldrum *et al.* 1983a, Cain *et al.* 1988, Loeb *et al.* 1990). APV inhibited metaphit-induced audiogenic seizures in a dose-related fashion. Low doses of APV preferentially influenced the latencies and duration of principal phases of the audiogenic seizure response, while leaving the incidence and severity of convulsions unaffected.

The potency of APV in our study differs from that reported for NMDA-induced convulsions in mice (Koek and Colpaert 1990). Co-administered i.c.v. with NMDA (0.31 μg), APV prevented seizures with ED_{50} of 0.19 μg (0.96 nmol), thus being about 100 times more potent in this model than in the metaphit model of AGS. The minimum dose of APV, which abolished seizures in DBA/2 mice, was 0.1 μmol (Meldrum *et al.* 1983a), while in the metaphit model of AGS a 3 times larger dose was required in rats. APV was 3-7 times more potent against running, clonus and tonus in DBA/2 mice. APV was shown to inhibit seizures induced by electrical stimulation of the amygdala in a dose within the range tested here (0.2 μmol, i.c.v.) (Cain *et al.* 1988). The different potency of APV in these models may be due to a different rate of diffusion from the ventricles, and due to a different contribution of excitatory neurotransmission and NMDA receptors in seizure initiation and propagation.

APH ((±)-2-amino-7-phosphonoheptanoic acid), another competitive NMDA antagonist, was 10 times more potent than APV in suppressing metaphit-induced audiogenic seizures, and 16-18 times more effective in blocking running, clonic and tonic convulsions (Zivanovic *et al.* 1997a).

Anticonvulsant action of APV was associated with behavioral side effects. The rapid appearance of ataxia after i.c.v. application suggests that the initial activity originate in structures close to the lateral ventricle. The anticonvulsant effect was not related to ataxia or decreased muscle tone, because they already disappeared at the time of next audiogenic testing. APV was able to antagonize convulsions in some models without any behavioral side-effects (Czuczwar *et al.* 1984, Loeb *et al.* 1990), while in others the anticonvulsant activity was accompanied by locomotor side-effects (Meldrum *et al.* 1983a, Koek and Colpaert 1990). This suggests that the behavioral effects of NMDA antagonists depend on the dose used, species and the route of administration.

The evaluation of EEG recordings suggested, however, that the metaphit-produced epileptiform EEG activity was refractory to APV, persisting even when there was a clear suppression of behavioral seizures. This probably reflects a high level of excitation still present, although insufficient to reach the „threshold" for overt seizures, and represented a prerequisite for the reappearance of behavioral convulsions. However, the i.c.v. injection of 0.3 μmol of APV in the absence of metaphit apparently induced epileptiform activity, but these discharges were restricted to a maximum of 40 min after the injection, while metaphit-induced EEG changes were observed for more than 24 h. This APV-induced epileptiform activity is in agreement with the finding that APV potentiated bursting in rat hippocampal slices (Dingledine *et al.* 1986). The same action on EEG in metaphit-treated rats was reported for APH (Zivanovic *et al.* 1997a. This action of competitive NMDA antagonists is in striking contrast to MK-801 ((5-methyl)-10,11-dibenzo(a,d)-cyclohepten-5,10-imine maleate), a non-competitive NMDA antagonist, which is reported to suppress both the EEG and behavioral convulsions produced by metaphit (Šušić *et al.* 1993). The blockade induced by these antagonist types is different: whereas MK-801 blocks NMDA-associated ion channels, APV and APH compete with the agonist for the NMDA recognition site. MK-801 blocks the NMDA response in a voltage- and use-dependent fashion. In order to effectively block NMDA-mediated transmission by MK-801, neuron would have to be exposed to the appropriate transmitter. Maximum exposure to the transmitter occurs during audio stimulation. It is possible that excessive release of transmitters during a loud sound stimulus opens ion channels and allows MK-801 to enter and block the channel, while APV and APH compete for NMDA recognition sites with an endogenous agonist. It

is reported that APV (160 and 40 mg/kg, i.p.) completely abolished both the spiking activity and myoclonic jerks induced by penicillin in rats (Loeb *et al.* 1990). The mechanism of action of these two convulsants may be the cause for different effects of APV on EEG, as well as the route of APV administration (i.c.v. versus i.p.).

In metaphit-induced audiogenic seizures, APV did not influence epileptic activity, but only its spreading into generalized convulsions, which suggests that APV is rather an anticonvulsant than an antiepileptic agent in this model of reflex epilepsy.

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References

AVOLI M, OLIVIER A: Bursting in human epileptogenic neocortex is depressed by an N-methyl-D-aspartate antagonist. *Neurosci Lett* **76:** 249-254, 1987.

BERGER P, JACOBSON AE, RICE KC, LESSOR RA, REITH MAE: Metaphit, a receptor acylator, inactivates cocaine binding sites in striatum and antagonizes cocaine-induced locomotor stimulation in rodents. *Neuropharmacology* **25:** 931-933, 1986.

CAIN DP, DESBOROUGH KA, McITRICK DJ.: Retardation of amygdala kindling by antagonism of NMD-aspartate and muscarinic receptors: evidence for the summation of excitatory mechanisms in kindling. *Exp Neurol* **100:** 179-187, 1988.

CHEN NH, WANG CD, JOBE PC, REITH MEA.: Facilitation of amygdala kindling development and kindling seizures by metaphit. *Epilepsia* **33:** 927-932, 1994.

CZUCZWAR SJ, TURSKI L, SCHWARZ M, TURSKI WA, KLEINROK Z: Effects of excitatory amino acid antagonists on the anticonvulsant action of phenobarbital or diphenylhydantoin in mice. *Eur J Pharmacol* **100:** 357-362, 1984.

DEBLER EA, LIPOVAC MN, LAJTHA A, ZLOKOVIC BV, JACOBSON AE, RICE KC, REITH MEA.: Metaphit, an isothiocyanate analog of PCP, induces audiogenic seizures in mice. *Eur J Pharmacol* **165:** 155-159, 1989.

DEBLER EA, LIPOVAC MN, LAJTHA A, ZLOKOVIC BV, DUNLOP DS, JACOBSON AE, RICE KC, DE COSTA B, REITH MEA: Metaphit-induced audiogenic seizures in mice. I. Pharmacologic characterization. *Epilepsia* **34:** 201-210, 1993.

DINGLEDINE R, HYNES MA, KING GL: Involvement of N-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. *J Physiol London* **380:** 175-189, 1986.

KOEK W, COLPAERT FC: Selective blockade of N-methyl-D-aspartate (NMDA)-induced convulsions by NMDA antagonists and putative glycine antagonists: relationship with phencyclidine-like behavioral effects. *J Pharmacol Exp Ther* **252:** 349-357, 1990.

PAXINOS G, WATSON C: *The Rat Brain in Stereotaxic Coordinates.* Academic Press, London, 1982.

LITCHFIELD JT, WILCOXON F: A simplified method of evaluating dose-effects experiments. *J Pharmacol Exp Ther* **96:** 99-113, 1949.

LOEB C, PATRONE A, BESIO G, BALESTINO M, MAINARDI P: The excitatory amino acid antagonist amino-phosphono-valeric acid (APV) provides protection against penicillin-induced epileptic activity in the rat. *Epilepsy Res* : 249-251, 1990.

MELDRUM BS, CROUCHER MJ, CZUCZWAR SJ, COLLINS JF, CURRY K, JOSEPH M, STONE TW: A comparison of the anticonvulsant potency of (±)2-amino-5-phosphonopentanoic acid and (±)2-amino-7-phosphonoheptanoic acid. *Neuroscience* **9:** 925-930, 1983a.

MELDRUM BS, CROUCHER MJ, BADMAN G, COLLINS JF: Antiepileptic action of excitatory amino acid antagonists in the photosensitive baboon, *Papio papio. Neurosci Lett* **39:** 101-104, 1983b.

RAFFERTY MF, MATTSON M, JACOBSON AE, RICE KC: A specific acylating agent for the [^{3}H]phencyclidine receptors in rat brain. *FEBS Lett* **181:** 318-322, 1985.

REITH MEA, JACOBSON AE, RICE KC, BENUCK M, ZIMANYI I: Effect of metaphit on dopaminergic neurotransmission in rat striatal slices: involvement of the dopamine transporter and voltage-dependent sodium channel. *J Pharmacol Exp Ther* **259:** 1188-1196, 1991.

SUSIC V, REITH MEA, ZLOKOVIC BV, LAJTHA A, JACOBSON AE, RICE KC, LIPOVAC MN: Electroencephalographic characteristics of audiogenic seizures induced in metaphit-treated small rodents. *Epilepsia* **32:** 783-790, 1991.

ŠUŠIĆ VT, MARKOVIĆ O, LIPOVAC MN: Metaphit-induced audiogenic seizure and its inhibition by MK-801: electroencephalographic and behavioral characterization. *Epilepsia* **34:** 8-17, 1993.

ZIVANOVIC D, SUSIC V, STANOJLOVIC O: APH, an N-methyl-D-aspartate receptor antagonist, blocks the metaphit-induced audiogenic seizures in rats. *J Physiol Paris* **91:** 317-323, 1997a.

ŽIVANOVIĆ D, STANOJLOVIĆ O, ŠUŠIĆ V: Metaphit-induced audiogenic seizures in rats and their inhibition by APV. *33rd Int Congr Physiol Sci*, St. Petersburg, 1997, abstr P010.14b.

Reprint requests

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