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Anticonvulsant and hypnotic effects of amiodarone

Gunnur OZBAKIS-DENGIZ[1], Aysegul BAKIRCI[2]

([1]*Department of Pharmacology, Medical Faculty, Karaelmas University, 67 600 Zonguldak, Turkey*)

([2]*Department of Infectious Diseases and Clinical Microbiology, Public Hospitals, 16 700 Karacabey-Bursa, Turkey*)

E-mail: gunnurozbakis@mynet.com; aysegulbakirci@mynet.com

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Abstract: Amiodarone hydrochloride is a potent anti-arrhythmic agent, known as a multiple ion-channel blocker in the heart. Although it has been detected in the rat brain, there are no data related to its central nervous system (CNS) effects. In this study, we evaluated anticonvulsant and hypnotic effects of amiodarone. Convulsions were induced by phentylenetetrazole (PTZ) (100 mg/kg) or caffeine (300 mg/kg) in mice. In both models, amiodarone prolonged both latency period and time to death, and acted as an anticonvulsant drug. It was found to be more effective in the PTZ model than in the caffeine model; none of the animals treated with 150 mg/kg dose amiodarone had died in the PTZ model. For hypnotic effect, sleeping was induced with pentobarbital (35 mg/kg) in rats. Amiodarone dose-dependently increased the sleeping time (677.7%~725.9%). In the sleeping test, all rats in 200 mg/kg amiodarone group died. In conclusion, anticonvulsant and hypnotic effects of amiodarone have shown the depressant effects on CNS. These effects may be dependent on its pharmacological properties.

Key words: Amiodarone, Phentylenetetrazole (PTZ), Caffeine, Convulsion, Sleeping
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INTRODUCTION

Amiodarone is a multiple ion-channel blocker drug, inhibiting sodium and calcium inward currents and potassium outward current, and having non-competitive adrenergic blocking effect (Kodama *et al*., 1999; Herbette *et al*., 1988; Roden, 2006). It is the most promising drug in the treatment of life-threatening ventricular tachyarrhythmias in patients with significant structural heart diseases (Kodama *et al*., 1999). It is highly lipid-soluble, is concentrated in many tissues, and has been shown to be detectable in the rat brain and to reach the highest concentration 20~30 min after intravenous administration (Wyss *et al*., 1990; Riva *et al*., 1982). However, studies related with its central nervous system (CNS) effects are still limited. Only one study reported that it increased the concentrations of γ-aminobutyric acid (GABA) and glycine and decreased those of aspartate and glutamate in rat medulla oblongata (Turovaya *et al*., 2005).

Inhibition or excitation of a neuron depends on concentrations of intracellular Ca^{2+} and Na^{+} and extracellular K^{+}, and also on balance between GABAergic and adenosinergic inhibitory transmissions and glutamatergic excitatory transmission. In epilepsy and sleeping, ion channels and neurotransmitters have important roles. Since amiodarone has multiple ion-channel blocker properties and increases the inhibitory neurotransmitters, in this study we wanted to investigate whether amiodarone has possible anticonvulsant effects in phentylenetetrazole (PTZ)- and caffeine-induced generalized convulsion models and whether it has possible hypnotic effect in pentobarbital-induced sleeping model.

MATERIALS AND METHODS

Animals

In the present study, male Swiss albino mice (25~35 g) and Sprague-Dawley rats (150~200 g) were used (Department of Pharmacology, Medical Faculty, Atatürk University, Erzurum, Turkey). Lighting operated on a 12-h dark:12-h light cycle, and temperature was maintained at 20~23 °C. The animals were left for 24 h to be accustomed to laboratory conditions

and were maintained on standard pellet diet and water ad libitum. Experimental procedures were induced between 09:00 and 12:00 a.m. to minimize the effect of circadian rhythm.

Experiments were performed in accordance with the recommendations from the Declaration of Helsinki (National Institutes of Health, 1986) and the internationally accepted principles in the care and use of experimental animals.

Drugs

Amiodarone hydrochloride (Sanofi, Turkey), PTZ (Sigma, USA), caffeine (Sigma, USA), diazepam (Deva, Turkey), and pentobarbital (Abbott, Turkey) used in the study were dissolved in distilled water, in a volume of 0.1 ml/10 g, intraperitoneally (i.p.).

PTZ- and caffeine-induced generalized convulsion models

Animals were separated as control, diazepam, and amiodarone groups. Distilled water was administrated i.p. to the control group, and diazepam and several doses (50, 100, 150 mg/kg) of amiodarone to the diazepam and the amiodarone groups, respectively. Then 30 min later PTZ (100 mg/kg) and caffeine (300 mg/kg) injections were given i.p. in all the groups. The doses of PTZ and caffeine, determined by preliminary study, caused the seizures beginning with the loss of righting reflex followed by a long tonus and the death in all animals. Soon after the PTZ and caffeine injections, the animals were individually placed in plastic cages for observation during 30 min for latency (the time period until the onset of the loss of righting reflex followed by a long tonus) and during 24 h for the time to death (the time period until the death) (Dhanabal *et al*., 2007), and these periods were measured as second(s). The convulsion rates and the mortality were also evaluated for each group.

Pentobarbital-induced sleeping time

Rat sleep was induced by the intraperitoneal administration of 35 mg/kg of pentobarbital. The animals received distilled water, diazepam, and 50, 100 and 200 mg/kg of amiodarone i.p. 30 min before pentobarbital administration. Latency time of sleep (time to loose the righting reflex) and sleeping time (duration of loss of the righting reflex) were recorded. Latency time as second (s) and sleeping time as minute (min) were measured (Dos Santos *et al*., 2005).

Statistical analysis

Data are presented as mean±*SEM* for each group in all figures. Results were evaluated by using post-hoc LSD test. For the analyses of the convulsion rates and the mortality, Fisher's exact test was used. $P<0.05$ was considered statistically significant.

RESULTS

Effects of amiodarone on the latency periods and the convulsion rates

For PTZ-induced convulsions, diazepam and amiodarone dose-dependently prolonged the latency periods, and these effects of both diazepam and 100~150 mg/kg amiodarone were statistically significant ($P<0.05$), as shown in Fig.1. While the convulsion rates were 100% in the control, diazepam, and 50 mg/kg amiodarone groups, these rates were 66.7% and 83.3% in 100 mg/kg and 150 mg/kg amiodarone groups, respectively; these results were not significant statistically ($P>0.05$), as shown in Table 1.

In the caffeine-induced convulsion model as shown in Fig.2, latency periods were prolonged by both diazepam and all doses of amiodarone, and these periods for diazepam and 100~150 mg/kg amiodarone were significantly different ($P<0.05$). In this model, the convulsion rates were 100% in all the groups (Table 2).

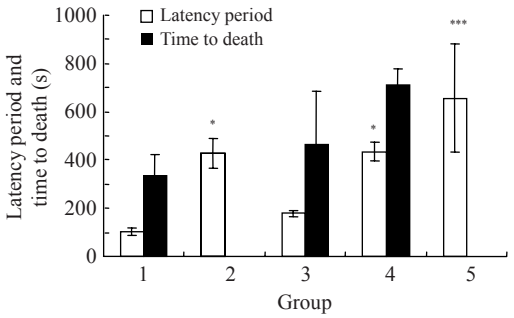

Fig.1 Effects of amiodarone on the latency periods and the time to death in the PTZ-induced convulsion model
Groups: 1: control; 2: 0.5 mg/kg diazepam; 3: 50 mg/kg amiodarone; 4: 100 mg/kg amiodarone; 5: 150 mg/kg amiodarone. For each group, $n=6$. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.005$ as compared with the control group (PTZ alone). Post-hoc LSD test was performed for the latency period and the time to death. All data are shown as mean±*SEM*

Table 1 Effects of amiodarone on the convulsion rate and the mortality in the PTZ-induced convulsion model

Group	Convulsion rate	Mortality
Control	6/6	6/6
0.5 mg/kg diazepam	6/6	0/6***
50 mg/kg amiodarone	6/6	3/6
100 mg/kg amiodarone	4/6	2/6*
150 mg/kg amiodarone	5/6	0/6***

Fisher's exact test was performed for the convulsion rate and the mortality. For each group, n=6. *P<0.05, **P<0.01, ***P<0.005 as compared with the control group (PTZ alone)

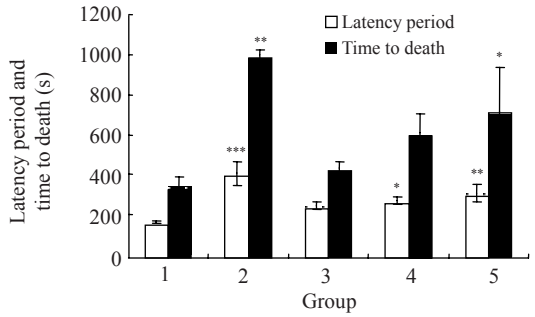

Fig.2 Effects of amiodarone on the latency period and the time to death in the caffeine-induced convulsion model

Groups: 1: control; 2: 5 mg/kg diazepam; 3: 50 mg/kg amiodarone; 4: 100 mg/kg amiodarone; 5: 150 mg/kg amiodarone. For each group, n=6. *P<0.05, **P<0.01, ***P<0.005 as compared with the control group (caffeine alone). Post-hoc LSD test was performed for the latency period and the time to death

Table 2 Effects of amiodarone on the convulsion rate and the mortality in the caffeine-induced convulsion model

Group	Convulsion rate	Mortality
Control	6/6	6/6
5 mg/kg diazepam	6/6	2/6*
50 mg/kg amiodarone	6/6	6/6
100 mg/kg amiodarone	6/6	6/6
150 mg/kg amiodarone	6/6	6/6

Fisher's exact test was performed for the convulsion rate and the mortality. For each group, n=6. *P<0.05, **P<0.01, ***P<0.005 as compared with the control group (caffeine alone)

Effects of amiodarone on the time to death and the mortality

Following the PTZ injections, since all mice in the diazepam and the 150 mg/kg amiodarone groups survived for 24 h, time to death of these groups was not presented in Fig.1. Amiodarone at 50 and 100 mg/kg doses had prolonged the time to death, but the difference was not statistically significant (P>0.05) in comparison to the control group. Following the PTZ injections, all mice in the control group had died, but the mortality in the amiodarone groups was reduced (Table 1), and this decrease for 100~150 mg/kg amiodarone groups was statistically significant (P<0.05). In this study, it was an interesting result that all animals in the 150 mg/kg amiodarone group remained alive in the 24 h observation period, similar to the diazepam group.

In the caffeine-induced convulsions (Fig.2), amiodarone dose-dependently prolonged the time to death in comparison to the control, but the effect at 150 mg/kg dose was statistically significant (P= 0.038), and all of the mice in the three amiodarone groups died, as in the control group (Table 2).

Effects of amiodarone on the pentobarbital-induced sleeping time test

In this study, diazepam shortened the latency time, and prolonged the sleeping time (444.4%). All doses of amiodarone had prolonged the latency time in comparison to the control and the diazepam groups (P<0.005), but dose-dependently shortened latency time. Amiodarone at doses of 50 and 100 mg/kg prolonged the sleeping time (677.7% and 725.9%, respectively, P=0.000) and all rats in the 200 mg/kg amiodarone group could not be awaken up and were all dead eventually (Fig.3).

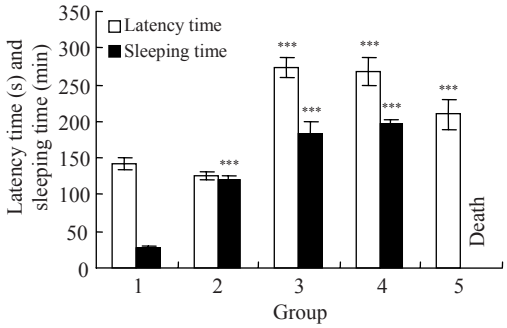

Fig.3 Effect of amiodarone on pentobarbital (35 mg/kg)-induced sleeping time test in rats

Groups: 1: control; 2: 1 mg/kg diazepam; 3: 50 mg/kg amiodarone; 4: 100 mg/kg amiodarone; 5: 200 mg/kg amiodarone. ***P<0.005 as compared with the control group (Post-hoc LSD test)

DISCUSSION

In the present study, amiodarone showed anticonvulsant and hypnotic effects, indicating that this

drug can behave as a CNS depressant. We induced the seizures with PTZ and caffeine in mice and sleep with pentobarbital in rats. PTZ-induced model, the most popular and widely used animal seizure model, represents a valid model for human generalized myoclonic and also absence seizures, and this test has been used primarily to evaluate anticonvulsant drugs (Loscher and Schmidt, 1988). Although convulsive activity of PTZ is not fully understood, it has been reported that PTZ has induced seizures by inhibiting GABA pathway in CNS (Corda *et al*., 1990; Macdonald and Baker, 1977), acting as an antagonist at GABA-A receptor complex (Yesilyurt *et al*., 2005), increasing the central noradrenergic activity (Corda *et al*., 1990; de Potter *et al*., 1980), and increasing the intracellular calcium and extracellular potassium ion concentrations (Heinemann *et al*., 1977; Onozuko *et al*., 1989; Piredda *et al*., 1985). As shown in the Fig.1, in the PTZ-induced model, amiodarone administrations prolonged the latency time and the time to death, and decreased the convulsion rates and the mortality. Especially, at 150 mg/kg dose, none of the animals died. Until now, amiodarone has been known and used as only an anti-arrhythmic drug. Recently, in addition to its anti-arrhythmic effect, we have shown its gastro-protective (Ozbakis-Dengiz *et al*., 2007a) and anti-inflammatory effects in histamine- and carrageenan-induced paw oedema models (Ozbakis-Dengiz *et al*., 2007b; Halici *et al*., 2007). In these reports (carrageenan-induced paw inflammation (Halici *et al*., 2007) and indomethacine-induced gastric ulcer models (Ozbakis-Dengiz *et al*., 2007a)), this drug had also presented an antioxidant activity and had caused a decrease in the catalase activity. It has been suggested that catalase stimulates the expressions of mRNA and the protein for cyclooxygenase-2 (COX-2) in rats' aortic smooth muscle cells, despite not affecting the expression of either mRNA or the protein for COX-1 (Ribeiro *et al*., 1997; Chen *et al*., 1998). We suggest that amiodarone may show the anti-inflammatory activity by inhibiting the COX-2 enzyme. Some researchers reported that some anti-inflammatory drugs (especially COX-2 inhibitors rofecoxib) had exhibited anticonvulsant effect (Kunz and Oliw, 2001; Gobbo and O′Mara, 2004; Dhir *et al*., 2008; Akula *et al*., 2008). Following PTZ-induced seizures, Takemiya *et al*.(2003) showed that COX-2 had induced prostaglandins and had enhanced levels of prostaglandin D_2 and prostaglandin E_2. In addition, Turovaya *et al*.(2005) reported that amiodarone had increased the concentrations of inhibitory GABA and glycine and had decreased those of excitatory aspartate and glutamate in rat medulla oblongata. In our study, the anticonvulsant effect of amiodarone in PTZ-induced seizures may be partially due to blockage of ion channels (Na^+, K^+ and Ca^{2+}) and/or its involvement in noradrenergic pathways and/or in GABAergic pathway and/or its anti-oxidant and anti-inflammatory effects (COX-2 inhibition).

Some anticonvulsant drugs act by means of ion channels. Anticonvulsant activities of calcium channel blockers had been shown in in vivo and in vitro experiments (Fischer, 1988; Kaminski *et al*., 2001). However, it has been reported that K^+ channel blockers precipitated seizure, and K^+ channel activators had anticonvulsant effects in some experimental seizure models (Kwan *et al*., 2001). In our study, amiodarone, known as a K^+ channel blocker, showed an anticonvulsant activity and we speculated that this drug showed this activity by inhibiting the outward K^+ currents at the neuron-like cardiac cells.

In this study, generalized convulsions were created with high dose caffeine, too. The mechanism of seizures is, however, still unclear. Most relevant to the pharmacological and toxicological effects of caffeine are (1) the blockade of adenosine receptors, (2) the inhibition of cyclic nucleotide phosphodiesterases, (3) the sensitization to calcium of the cyclic adenosine diphosphate ribose-modulated calcium-release channel associated with certain intracellular stores of calcium, (4) the inhibition of inhibitory GABA-A and glycine receptors, and (5) the enhancement of *N*-methyl-D-aspartic acid (NMDA) receptor neurotransmission (Daly, 2000; Harinath and Sikdar, 2005). As shown in Fig.2 and Table 2, in the caffeine model, although amiodarone had no effect on the convulsion rates and the mortality, it had prolonged the latency time and the time to death; amiodarone was more effective in the PTZ model than in the caffeine model. Since caffeine-induced seizure is not mainly related to ion channels, we speculate that amiodarone may prevent the adenosine receptor blockage and/or the GABA-A receptor blockage and/or the enhancement of NMDA receptor neurotransmission.

We have also shown that amiodarone prolonged the sleeping time and behaved as CNS depressant

drug in pentobarbital-induced sleeping model (Fig.3). This drug is highly lipid-soluble, and had been shown to pass into the brain (Wyss *et al*., 1990; Riva *et al*., 1982) and also to increase the concentrations of GABA and glycine (Turovaya *et al*., 2005); thus we may speculate that this drug had shown synergic effect with pentobarbital. Ohtsuka *et al*.(2006) reported that barbiturates used as anticonvulsant drug at high concentrations but not at clinically relevant concentrations inhibited ATP-sensitive K^+ channel (K_{ATP}) channels activated by intracellular ATP depletion in rat substantia nigra, and Holmes *et al*.(2000) reported that amiodarone inhibited the K_{ATP} channels. In this section, all animals in the high dose amiodarone group had died; thus, we may suggest that amiodarone has potentiated the effect of pentobarbital on the K_{ATP} channels.

CONCLUSION

In this study, we have presented that amiodarone had an anticonvulsant and hypnotic effects, that none of the animals died at 150 mg/kg dose in the PTZ-induced seizure model, and that all of the animals at 200 mg/kg dose of amiodarone died in sleeping test. These results indicate that amiodarone has CNS effects, especially central depressant effects; however, further studies are necessary to investigate its anticonvulsant and hypnotic profiles, and other effects on CNS. In addition we also suggest that clinicians be cautious while using amiodarone in combination with other CNS depressants.

References

Akula, K.K., Dhir, A., Kulkarni, S.K., 2008. Rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor increases pentylenetetrazol seizure threshold in mice: possible involvement of adenosinergic mechanism. *Epilepsy Res.*, **78**:60-70. [doi:10.1016/j.eplepsyres.2007.10.008]

Chen, G., Kamal, M., Hannon, R., Warner, T.D., 1998. Regulation of cyclooxygenase gene expression in rat smooth muscle cells by catalase. *Biochemical Pharmacology*, **55**(10):1621-1631. [doi:10.1016/S0006-2952(98)00021-5]

Corda, M.G., Giorgi, O., Longoni, B., Orlandi, M., Biggio, G., 1990. Decrease in the function of the γ-aminobutyric acid-coupled chloride channel produced by the repeated administration of pentylenetetrazol to rats. *J. Neurochem.*, **55**(4):1216-1221. [doi:10.1111/j.1471-4159.1990.tb03127.x]

Daly, J.W., 2000. Alkylxanthines as research tools. *J. Auton. Nerv. Syst.*, **81**(1-3):44-52. [doi:10.1016/S0165-1838(00)00110-7]

de Potter, W.P., de Potter, R.W., de Smett, F.H., de Schaepdryver, A.F., 1980. The effect of drugs on the concentration of dopamine β-hydroxylase in the cerebrospinal fluid of rabbits. *Neuroscience*, **5**(11):1969-1977. [doi:10.1016/0306-4522(80)90042-1]

Dhanabal, S.P., Paramakrishnan, N., Manimaran, S., Suresh, B., 2007. Anticonvulsant potential of essential oil of artemisia abrotanum. *Curr. Trends Biotechnol. Pharm.*, **1**(1):112-116.

Dhir, A., Akula, K.K., Kulkarni, S.K., 2008. Rofecoxib potentiates the anticonvulsant effect of topiramate. *Inflammopharmacology*, **16**(2):83-86. [doi:10.1007/s10787-007-7007-6]

Dos Santos, J.G.Jr., Blanco, M.M., Do Monte, F.H.M., Russi, M., Lanziotti, V.M.N.B., Leal, L.K.A.M., Cunha, G.M., 2005. Sedative and anticonvulsant effects of hydroalcoholic extract of *Equisetum arvense*. *Fitoterapia*, **76**(6):508-513. [doi:10.1016/j.fitote.2005.04.017]

Fischer, W., 1988. Antiepileptic effect of calcium antagonist. *Drugs Today*, **24**:167-174.

Gobbo, O.L., O′Mara, S.M., 2004. Post-treatment, but not pretreatment, with the selective cyclooxygenase-2 inhibitor celecoxib markedly enhances functional recovery from kainic acid-induced neurodegeneration. *Neuroscience*, **125**(2):317-327. [doi:10.1016/j.neuroscience.2004.01.045]

Halici, Z., Ozbakis-Dengiz, G., Odabasoglu, F., Suleyman, H., Cadirci, E., Halici, M., 2007. Amiodarone has anti-inflammatory and anti-oxidative properties: an experimental study in rats with carrageenan-induced paw edema. *Eur. J. Pharmacol.*, **566**(1-3):215-221. [doi:10.1016/j.ejphar.2007.03.046]

Harinath, S., Sikdar, S.K., 2005. Inhibition of human TREK-1 channels by caffeine and theophylline. *Epilepsy Res.*, **64**(3):127-135. [doi:10.1016/j.eplepsyres.2005.03.002]

Heinemann, U., Lux, H.D., Gutnick, M.J., 1977. Extracellular free calcium and potassium during paroxysmal activity in the cerebral cortex of the cat. *Exp. Brain Res.*, **27**(3-4):237-243. [doi:10.1007/BF00235500]

Herbette, L.G., Trumbore, M., Chester, D.W., Katz, A.M., 1988. Possible molecular basis for the pharmacokinetics and pharmacodynamics of three membrane-active drugs: propranolol, nimodipine and amiodarone. *J. Mol. Cell. Cardiol.*, **20**(5):373-378. [doi:10.1016/S0022-2828(88)80128-7]

Holmes, D.S., Sun, Z.Q., Porter, L.M., Bernstein, N.E., Chinitz, L.A., Artman, M., Coetzee, W.A., 2000. Amiodarone inhibits cardiac ATP-sensitive potassium channels. *J. Cardiovasc. Electrophysiol.*, **11**(10):1152-1158. [doi:10.1111/j.1540-8167.2000.tb01762.x]

Kaminski, R.M., Mazurek, M., Turski, W.A., Kleinrok, Z., Czuczwar, S.J., 2001. Amlodipine enhances the activity of antiepileptic drugs against penthylenetetrazole-induced seizures. *Pharmacol. Biochem. Behav.*, **68**(4):661-668. [doi:10.1016/S0091-3057(01)00468-3]

Kodama, I., Kamiya, K., Toyama, J., 1999. Amiodarone: ionic and cellular mechanisms of action of the most promising

class III agent. *Am. J. Cardiol.*, **84**(9):20R-28R. [doi:10.1016/S0002-9149(99)00698-0]

Kunz, T., Oliw, E.H., 2001. The selective cyclooxygenase-2 inhibitor rofecoxib reduces kainate-induced cell death in the rat hippocampus. *Eur. J. Neurosci.*, **13**(3):569-575. [doi:10.1046/j.1460-9568.2001.01420.x]

Kwan, P., Sills, G.J., Brodie, M.J., 2001. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacology & Therapeutics*, **90**(1):21-34. [doi:10.1016/S0163-7258(01)00122-X]

Loscher, W., Schmidt, D., 1988. Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. *Epilepsy Res.*, **2**(3):145-181. [doi:10.1016/0920-1211(88)90054-X]

Macdonald, R.L., Baker, J.L., 1977. Pentylelnetetrazol and penicillin are selective antagonists of GABA-mediated post-synaptic inhibition in cultured mammalian neurons. *Nature*, **267**(5613):720-721. [doi:10.1038/267720a0]

National Institutes of Health, 1986. Guide for the Care and Use of Laboratory Animals. DHEW Publication No. 86-23, US Government Printing Office, Washington, DC.

Ohtsuka, T., Ishiwa, D., Kamiya, Y., Itoh, H., Nagata, I., Saito, Y., Yamada, Y., Sumitomo, M., Andoh, T., 2006. Effects of barbiturates on ATP-sensitive K^+ channels in rat substantia nigra. *Neuroscience*, **137**(2):573-581. [doi:10.1016/j.neuroscience.2005.08.078]

Onozuko, M., Nakagaki, I., Sasaki, S., 1989. Petylenetetrazole-induced seizure activity produces an increased release of calcium from endoplasmic reticulum by mediating cyclic AMP-dependent protein phosphorylation in rat cerebral cortex. *Gen. Pharmacol.*, **20**:627-634.

Ozbakis-Dengiz, G., Odabasoglu, F., Halici, Z., Suleyman, H., Cadirci, E., Bayir, Y., 2007a. Gastroprotective and antioxidant effects of amiodarone on indomethacin-induced gastric ulcers in rats. *Arch. Pharm. Res.*, **30**(11):1426-1434. [doi:10.1007/BF02977367]

Ozbakis-Dengiz, G., Halici, Z., Akpinar, E., Cadirci, E., Bilici, D., Gursan, N., 2007b. Role of polymorphonuclear leukocyte infiltration in the mechanism of anti-inflammatory effect of amiodarone. *Pharmacol. Rep.*, **59**(5):538-544.

Piredda, S., Yonekawa, W., Whittingham, T.S., Kupferberg, H.J., 1985. Potassium, pentylenetetrazole, and anticonvulsants in mouse hippocampal slices. *Epilepsia*, **26**(2):167-174. [doi:10.1111/j.1528-1157.1985.tb05401.x]

Ribeiro, S.M.R., Campello, A.P., Nascimento, A.J., Kluppel, L.W., 1997. Effect of amiodarone (AMD) on the antioxidant enzymes, lipid peroxidation and mitochondrial metabolism. *Cell Biochem. Funct.*, **15**(3):145-152. [doi:10.1002/(SICI)1099-0844(199709)15:3<145::AID-CBF728>3.0.CO;2-X]

Riva, E., Gerna, M., Neyroz, P., Urso, R., Bartosek, I., Guaitani, A., 1982. Pharmacokinetics of amiodarone in rats. *J. Cardiovasc. Pharmacol.*, **4**(2):270-275. [doi:10.1097/00005344-198203000-00016]

Roden, D.M., 2006. Antiarrhytmic Drugs. *In*: Brunton, L.L., Lazo, J.S., Parker, K.L. (Eds.), Goodman & Gilman's: The Pharmacological Basis of Therapeutics. The McGraw-Hill Companies, New York, USA, p.899-932.

Takemiya, T., Suzuki, K., Sugiura, H., Yasuda, S., Yamagata, K., Kawakami, Y., Maru, E., 2003. Inducible brain COX-2 facilitates the recurrence of hippocampal seizures in mouse rapid kindling. *Prostaglandins & Other Lipid Mediators*, **71**(3-4):205-216. [doi:10.1016/S1098-8823(03)00040-6]

Turovaya, A.Y., Galenko-Yaroshevskii, P.A., Kade, A.K., Uvarov, A.E., Kiguradze, M.I., Khvitiya, N.G., Tatulashvili, D.R., 2005. Effects of verapamil and amiodarone on sympathoadrenal system and balance of excitatory and inhibitory amino acids in rat medulla oblongata. *Bull. Exp. Biol. Med.*, **139**(6):665-667. [doi:10.1007/s10517-005-0372-5]

Wyss, P.A., Moor, M.J., Bickel, M.H., 1990. Single-dose kinetics of tissue distribution, excretion and metabolism of amiodarone in rats. *J. Pharmacol. Exp. Ther.*, **254**:502-507.

Yesilyurt, O., Dogrul, A., Uzbay, T., 2005. Differential effects of systemic versus central routes of administration of L-type calcium channel blockers on pentylenetetrazole-induced seizures in mice. *Bull. Clin. Psychopharmacol.*, **15**(4):153-157.