Journal of Clinical Medicine and Research Vol. 4(7), pp. 89-93, October, 2012
Available online http://www.academicjournals.org/JCMR
DOI: 10.5897/JCMR12.003
ISSN 2141-2235 ©2012 Academic Journals

Full Length Research Paper

The effect of furosemide on experimentally-induced seizures in mice

S. E. Oriaifo[1]*, I. Otokiti[2] and E. K. Omogbai[2]

[1]Department of Pharmacology, College of Medicine, Ambrose Alli University, Ekpoma, Edo State, Nigeria.
[2]Department of Pharmacology, University of Benin, Benin-City, Edo State, Nigeria.

Accepted 10 April, 2012

The aim of this study was to investigate the effect of the loop diuretic, furosemide, on maximal electroshock- and leptazol-induced seizures in mice. Mice were given furosemide, phenytoin and diazepam intraperitoneally and after 30 min they were challenged with maximal electroshock (MES) or leptazol. In MES, furosemide at doses of 25 and 50 mg/kg did not protect against hind limb tonic extension (HLTE) while phenytoin (25 mg/kg) provided protection against HLTE. Furosemide at doses of 25 and 50 mg/kg afforded protection against leptazol-induced Racine stage 4 seizures ($P < 0.05$), but 100% (all the animals in a group surviving) protection was only provided at 30 min by the 50 mg/kg dose. Diazepam at 2 mg/kg did not offer 100% protection at 30 min. Results provide evidence that furosemide is effective against leptazol-induced seizures, but not against maximal electroshock-induced seizures; and the present results suggest that furosemide is more potent than diazepam against leptazol-induced seizures.

Key words: Furosemide, phenytoin, diazepam, maximal electroshock (MES), leptazol, seizures.

INTRODUCTION

The maximal electroshock (MES) is a useful tool for evaluating generalized tonic-clonic (grand mal) seizures (Territo et al., 2007). In mice, MES-induced seizures consist of initial tonic flexion, then hind limb tonic extension (HLTE), followed by the stage of clonus and terminal stupor. The endpoint of efficacy is taken as inhibition or abolition of HLTE (Naveen et al., 2011; Porter et al., 1984). Pentylenetetrazol (also known as leptazol or PTZ) at high doses interacts with the picrotoxin site of the gamma-amino butyric acid$_A$ (GABA$_A$) receptor to inhibit the specific binding of GABA and cause convulsions. Leptazol-induced convulsion is now known to lead to widespread hippocampal apoptotic neuronal cell death by activation of caspase-3 (Nasser et al., 2009). Though leptazol-induced convulsions may be considered as more characteristic of grand-mal, the leptazol (PTZ) seizure model is also considered valid for human generalized myoclonic and absence seizures (Kumar and Madhab, 2011; Kent and Webster, 1983). Four stages of PTZ-induced seizures (Racine, 1972) are generally recognized: (0) no seizure; (1) stage of facial automatisms; (2) stage of head nodding and jerks; (3) stage of forelimb clonus; (4) stage of rearing and falling with forelimb clonus (generalized motor seizures) which may be taken to be the endpoint of efficacy. Phenytoin, by its stabilization of the sodium channel in the inactive state and by its inhibition of the calcium channel, blocks and prevents post-tetanic potentiation, limits development of maximal seizure activity and reduces the spread of seizures (Sankar and Holmes, 2004); attributes that have made it useful also for leptazol-induced seizures (Leach et al., 1991). Phenytoin can also cause reciprocal

*Corresponding author. E-mail: pravee.21msc@gmail.com.

Abbreviations: MES, maximal electroshock; **GABA,** gamma-amino butyric acid; **NKCC$_1$,** isoform 1 of the Na_+-K_+-2Cl co-transporter; **KCC$_2$,** isoform 2 of the K_+-2Cl co-transporter; **BDNF,** brain-derived neurotrophic factor; **TrkB,** tropomyosin-related tyrosine kinase receptor B; **NMDA,** N-methyl-$_D$-aspartate; **ECS,** extra-cellular space; **NADPH,** nicotinamide adenine dinucleotide phosphate hydrogen; **SD,** standard deviation; **ANOVA,** analysis of variance.

modulation of glutamate and GABA release which leads to simultaneous reduction in synaptic excitation and an increase in inhibition in cortical networks (Cunningham et al., 1999). Phenytoin may paradoxically facilitate epileptogenesis and precipitate absence seizures since it may indirectly increase hypersynchronisation of neuronal discharges (Murthy, 2011). Diazepam, which enhances GABAergic mechanisms, has been found to be protective, alone or in combination, against leptazol-induced seizures (Billimoria et al., 1981) and MES-induced seizures (Srivastava and Gupta, 2001). Investigators have hinged the anti-epileptic actions of furosemide on its diuretic mechanisms (Hesdorffer et al., 2001; Holtkamp et al, 2003). Plausible as this seemed, it did not explain the magnitude of furosemide's antiepileptic action as compared to other carbonic anhydrase-inhibiting diuretics, such as acetazolamide (Staley, 2002) or cation-chloride co-transporter blocking diuretics, such as bumetanide (Margineau and Klitgaard, 2006). Moreover, the antiepileptic effect of furosemide has not been related to a change in CSF osmolality as it is the case with mannitol (Stringer and Pan, 1997). Furosemide may interfere with the packaging of the excitatory neurotransmitter, glutamate, into synaptic vesicles reducing the ability of a nerve terminal to release glutamate. Furosemide could also interfere with glial glutamate transport, reducing glial-neuronal glutamate recycling necessary for sustained synaptic transmission (Staley et al., 1998). Furosemide blocks the inwardly directing cation-chloride co-transporter, $NKCC_1$, at lower micromolar concentrations than for the outwardly directing cation chloride co-transporter, KCC_2 (Friauf et al., 2011). This blocking effect of high doses of furosemide on KCC_2 has the same time-course as low chloride solution in decreasing epileptic activity (Hochman et al., 1999), inferring that prevention of neuronal extrusion of [Cl-] by KCC_2-blockers may result in decreases in $[Cl-]_o$ that can be anti-epileptogenic, while the blocking action of furosemide on $NKCC_1$ may decrease cell volume and increase extracellular space that is shrinked by ictal episodes probably mediated by the epileptogenicity of tropomysin-related tyrosine kinase $receptor_B$ (TrkB), the brain-derived neurotrophic factor (BDNF) receptor (He et al., 2004). Additionally, furosemide may synergise with BDNF in the induction of neuropeptide Y release which is one of the neuromodulators involved in seizure termination (Lado and Moshe, 2008).

The aim of this study was to evaluate the effect of the loop diuretic, furosemide, in the PTZ and MES models of epilepsy in mice and to compare its anticonvulsant effect with that of diazepam in the PTZ model and with phenytoin in the MES model.

MATERIALS AND METHODS

Male albino mice (20 to 40 g) were allowed to acclimatize in the University's Animal House for two weeks before they were divided into groups of 6 mice each in separate labeled cages for control (0.2 ml of 10% Tween 80), furosemide at doses of 25 and 50 mg/kg; phenytoin at a dose of 25 mg/kg and diazepam, at dose of 2 mg/kg. They were then transported to the Laboratory and one hour elapsed before the injections were given intra-peritoneally (ip).

PTZ-induced seizures

In this model, the effects of the control group, the diazepam groupand the furosemide groups were compared. The injections were given intra-peritoneally as stated earlier. After 30 min, 70 mg/kg of pentylenetetrazol (leptazol) was administered ip. Animals were observed for onset and character of myoclonic spasms and tonic-clonic convulsions (Racine stage 4 generalized motor seizures) up to 60 min after leptazol injection. The animals could convulse and recover (when protection is assumed) or convulse and die. 100% protection is assumed if no animal in the group convulses and dies. Arumugam et al. (2009) reported that the percentage of prevention of mortality in a group of rodents (n = 6) was a useful index of protection by antiseizure agents. Latency was determined by the time needed for the development of unequivocal sustained seizure activity which is Racine stage 4 (Khosla and Pandhi, 2001).

MES-induced seizures

In another related experiment, groups of mice with 6 in each group were given same doses of control injection, Furosemide and phenytoin. After 30 min, maximal electroshock was delivered by a Rodent Shocker convulsiometer through ear clips. Seizure induction was by alternating current of 50 mA and stimulus duration was 0.2 s. Animals were observed closely for 2 min for duration or abolition of HLTE which was the endpoint of efficacy and an indication of seizure prevention (Browning, 1992). Drugs were purchased from Sigma-Aldrich via Rovet Chemicals, Benin-City.

Statistical analysis

Results are expressed in seconds (s) ± standard deviation (SD). Mann-Whitney non-parametric test was used to compare two groups for significant difference and was considered significant if $P < 0.05$. Analysis of variance (ANOVA) was used for multiple sample analysis followed by post-hoc Tukey's test and $P < 0.05$ was taken to be significant difference.

RESULTS

Table 1 shows that there is a significant dose-response relationship to furosemide $F(2, 15) = 14.35$, ($P < 0.05$). Effect was maximal with the 50 mg/kg dose against leptazol-induced seizures which provided 100% protection as compared to the 66.6% protection provided by diazepam. Period of onset of Racine stage 4 convulsions with furosemide was dose-dependent.

In the MES model of epileptic seizures, none of the furosemide dosage provided protection while the phenytoin dose provided 100% protection against MES-induced seizures; but the furosemide doses reduced the duration of HLTE significantly ($P < 0.05$) as compared to controls (Table 2).

Table 1. Effect of Furosemide and Diazepam on Leptazol-Induced Seizures at 30 min.

Group	Seizure onset (s ± SD)	P	Protection (%)	Mortality (%)
Control				
0.2 ml	20.5 ± 2.3		0	100
Furosemide				
25 mg/kg	82.00 ± 1.8	<0.05	50	50
50 mg/kg	100.00 ± 3.00	< 0.05	100	0
Diazepam				
2 mg/kg	100.5 ± 3.1	< 0.05	66.6	33.3

Order of magnitude of response was furosemide > diazepam. The effect of furosemide, maximal at 50 mg/kg, was dose-dependent and the difference in period of onset of seizures (latency) between test and control groups was statistically significant ($P < 0.05$). 100% protection is assumed if no animal in a group convulses and dies.

Table 2. Effect of Furosemide and Phenytoin on MES -Induced Seizures at 30 min.

Group	Mean duration of HLTE (s ± SD)	Protection (%)	Mortality (%)
Control			
0.2 ml	16.5 ± 3.5	0	100
Furosemide			
25 mg/kg	12.0 ± 4.6 ($P < 0.05$)	0	100
50 mg/kg	6.3 ± 3.9 ($P < 0.05$)	0	100
Phenytoin			
20 mg/kg	0 ($P < 0.05$)	100	0

At the chosen doses, furosemide offered no protection to mice against MES-induced seizures; but reduced the duration of HLTE significantly compared to control ($P < 0.05$) which was dose-dependent. 0% protection is assumed if no animal in a group survives the convulsive episodes.

DISCUSSION

The experimental results confirm the only previous work on the protective action of furosemide against leptazol-induced seizures by Kielczewska-Mrozikiewicz (1968). The present result, also, is in agreement with the previous report (Luszczki et al., 2007) that furosemide did not protect mice against MES-induced convulsions and is at variance with the report of Hesdorffer et al. (2001) that the diuretic, furosemide, provided protection against MES-induced seizures. Our results showed that furosemide is, nevertheless, able to reduce the duration of HLTE of MES-induced seizures and this may be responsible for its potentiation of valproate against MES-induced seizures reported by Luszczki et al. (2007). Further work may be necessary to determine the differential effect between furosemide and bumetanide, another loop diuretic, and between furosemide and a calcium channel blocker, such as nifedipine, that modulates NMDA receptor function so as to shed more light on the mechanism of action of furosemide in protecting mice against leptazol-induced convulsions.

The sodium-potassium-chloride co-transporter inhibitor, furosemide, has been found recently to possess a wide spectrum of activity which includes anticonvulsant activity. An emerging body of evidence points to the efficacy of furosemide as a neurochemical with neuroprotective effects (Ahmad et al., 1976, 1977). A primary mechanistic explanation for furosemide's ability to terminate seizures may be its ability to prevent sustained Ca^{2+} intracellular increases due to hyperglutamatergic excitotoxicity (Sanchez-Gomez et al., 2011), a property it now seems to share with other NMDA receptor antagonists, such as the calcium channel blockers (Palmer et al., 1993). Besides, furosemide, which induces BDNF release (Szekeres et al., 2010), may enhance the seizure-terminating effect of neuropeptide Y (Binder et al., 2001) which is upregulated by BDNF. Furthermore, changes in chloride transporter expression contribute to human epileptiform activity (Huberfeld et al., 2007) with increased sodium-potassium-chloride cotransporter ($NKCC_1$) and altered

distribution of the neuron-specific potassium-chloride cotransporter (KCC_2) (Reid et al., 2000; Aronica et al., 2007), and molecules such as furosemide acting on these transporters may be useful antiepileptic drugs. Reid et al. (2000) had suggested that the KCC_2 co-transporter may be upregulated in those instances, such as global ischaemia when the loop diuretics which are blockers of the co-transporter may be effective in terminating seizures. Modulation of electrical field interactions via the extra-cellular space (ECS) might also contribute to neuronal hypersynchrony and epileptogenicity and present evidence suggesting that non-synaptic mechanisms play a critical role in modulating the epileptogenicity of the human brain. Furosemide and other drugs that modulate the extra-cellular space (Gutschmidt et al, 1999; Hochman et al, 1999; Hochman et al, 1995) might possess clinically useful antiepileptic properties, while avoiding the side-effects associated with the suppression of neuronal excitability (Haglund and Hochman, 2005) being exhibited by drugs, such as the 1, 4-benzodiazepines.

Studies have also shown that furosemide can reversibly suppress low Ca^{2+}-induced and low Mg^{2+}-induced epileptiform activity. Amplitudes of evoked field potentials underwent an initial slight increase followed by a significant reduction after prolonged furosemide treatment. Furosemide more potently blocks leptazol-induced epileptiform activity in our experiments than diazepam. Endogeneous field effects in the CNS play functional roles and they are thought to contribute to epileptogenesis (Weiss and Faber, 2010) and there is evidence for a role of field effects (ephaptic transmission) in rhythmogenesis in cortex and hippocampus (Buzsaki, 2002). The administration of furosemide suppresses leptazol-induced epileptic activity potently in the human cortex probably by also reducing field effect interactions (ephaptic transmission) (Haglund and Hochman, 2005; Weiss and Faber, 2010; Dudek et al., 1989) more than diazepam.

Recent studies have shown evidence that the persistently high levels of brain-derived neurotrophic factor (BDNF) engendered by ictal activity may be pro-necrotic through activation of NADPH oxidase (Kim et al., 2002; Park et al., 2006) and that the Bcl-2-associated protein X (Bax) blocker furosemide (Lin et al., 2005) which is anti-apoptotic may serve in this instance as a neuroprotective. Also, since oxidative stress (Ikonomidou, 2002), inflammatory mediators and hyperglutamatergic excitotoxicity too underlie epileptogenesis and epileptic brain injury, antioxidants such as furosemide (Hamelink et al., 2005) may play a greater role in future in preventing neurodegeneration from being a cause of and sequel of epilepsy (Vercueil, 2004; Koyama and Ikegaya, 2005).

In conclusion, the present experimental results show that furosemide significantly and dose-dependently suppressed leptazol-induced convulsions in mice and displayed no protective effect against MES-induced seizures in this *in vivo* study.

REFERENCES

Ahmad S, Clarke L, Hewett AJ, Richens A (1976). Controlled trial of frusemide as an antiepileptic drug in focal epilepsy. Br. J. Clin. Pharmacol. 3(4):621-625.

Ahmad S, Perucca E, Richens A (1977). The effect of Furosemide, mexilente, (+)- propranolol and three benzodiazepine drugs on interictal spike discharges in the electroencephalogram of epileptic patients. Br. J. Clin. Pharmacol. 4:683-688.

Aronica E, Boer K, Redaku S, Spliet WGM, van Rijen PC, Troost D, Gorter JA (2007). Differential expression patterns of chloride transporters, Na-K-2Cl cotransporters and K-Cl cotransporters in epilepsy-associated malformations of cortical development. Neuroscience 145:185-196.

Arumugam S, Palanivelu A, Retnasany G, Ramaiyan D (2009). Study on the antiseizure activities of inner bark of *Guettarda speciosa* (L). Iran. J. Pharmacol. Therap. 8:73-76.

Billimoria RB, Naik PR, Satoskar RS (1981). Effect of diazepam alone or in combination with chlorpromazine or propranolol in experimentally-induced convulsions in mice. JPGM 27(2):73-79.

Binder DK, Croll SD, Gall C, Scharfman HE (2001). BDNF and epilepsy: Too much of a good thing. Trends Neurol. 24(1):47-53.

Browning R (1992). The electroshock model, neuronal network and antiepileptic drugs. In: Drugs for control of epilepsy: Actions on neuronal networks in seizure disorders. (Faingold CL and Fromm GH, Eds). CRC Press. pp. 195-211.

Buzsaki G (2002). Theta oscillations in the hippocampus. Neuron 33:325-340

Cunningham MO, Dhillon A, Wood SJ, Jones RSG (1999). Reciprocal modulation of glutamate and GABA release may underlie the anticonvulsant effect of phenytoin. Neuroscience 96(2):343-351.

Dudek FE, Yasumura H, Rash JE (1989). Non-synaptic mechanisms in seizures and epileptogenesis. Cell Biol. Int. 22:793-805.

Friauf E, Rust MB, Schulenborg T, Hirtz J (2011). Chloride transporters, chloride homeostasis and synaptic inhibition in the developing auditory system. Hearing Res. 279:96-110.

Gutschmidt KU, Stenkamp K, Buchherm K (1999). Anticonvulsant actions of furosemide *in vitro*. Neuroscience 91(4):1471-1481.

Haglund MM, Hochman DW (2005). Furosemide and mannitol suppression of epileptic activity in the human brain. J. Neurophysiol. 94:907-918.

Hamelink C, Hampson A, Wink DA, Eiden LE, Eskay RL (2005). Comparison of cannabidiol, antioxidants and diuretics in reversing binge ethanol-induced neurotoxicity. JPET 314(2):780-788.

He X-P, Kotioski K, Nef S, Luikart BW, Parada CF, McNamara JO (2004). Conditional deletion of TrkB but not BDNF prevents epileptogenesis in the kindling model. Neuron 43:31-42.

Hesdorffer DC, Stables JP, Hauser WA (2001). Are certain diuretics also anticonvulsants. Ann. Neurol. 50:458-462.

Hochman DW, Baraban SC, Owen JWN, Schwartzkroin PA (1995). Dissociation of synchronization and excitability in furosemide blockade of epileptiform activity. Science 270(5233):99-102.

Hochman DW, D'Ambrosia R, Janigro D, Schwartzkroin PA (1999). Extracellular chloride and the maintenance of spontaneous epileptiform activity in rat hippocampal slices. J. Neurophysiol. 81:49-59.

Holtkamp M, Matzen J, Buchhein K, Walker MC (2003). Furosemide terminates limbic status epilepticus in freely moving rats. Epilepsia 4(9):1141-1144.

Huberfeld G, Wittner L, Clemenceau S, Baulac M, Kaila K, Miles R, Rivera C (2007). Perturbed chloride homeostasis and GABAergic signaling in human temporal lobe epilepsy. J. Neurosci. 27(37):9866-9873.

Ikonomidou C (2002). Neurodegeneration and neuroprotection in the epileptic brain. Ann. gen. psychiatry 7(suppl 1): S73. International Society on Brain and Behaviour,3rd International Congress on Brain and Behaviour; Thessalonika, Greece 28 Nov-2 Dec. 2002.

Kent AP, Webster RA (1983). The evaluation of different types of anti-convulsant drug activity against leptazol-induced epileptogenic activity in the anaesthetized rat. Br. J. Pharmacol. 78:553-559.
Khosla P, Pandi P (2001). Anticonvulsant effect of nimodipine alone and in combination with diazepam on pentylenetetrazol-induced status epilepticus. Indian J. Pharmacol. 33:208-211.
Kielczewska-Mrozikiewicz D (1968). Experimental studies on the effect of lasix on the occurrence of cardiazol convulsions. Przeglad Lekarski 24:716-718.
Kim SH, Won SJ, Sohn S, Kwon HJ, Lee JY, Park JH, Gway BL (2002). BDNF can act as a pro-necrotic factor through transcriptional and translational activation of NADPH oxidase. JCB., 159(5):821-831.
Koyama R, Ikegaya Y (2005). To BDNF or not to BDNF: That is the epileptic hippocampus. Neuroscientist 11(4):282-287.
Kumar RS, Madhab KG (2011). An experimental evaluation of anticonvulsant activity of Nerium oleander leaf extract. Int. Res. J. Pharmacol. 2(10):73-75.
Lado FA, Moshe SL (2008). How do seizures stop? Epilepsia 49(10):1651-1664.
Leach MJ, Baxter MG, Critchley MA (1991). Neurochemical and behavioral aspects of lamotrigine. Epilepsia 32(Suppl. 2):S4-8.
Lin CH, Lu YZ, Cheng FC, Chu LF, Hsueh CM (2005). Bax-regulated mitochondrial translocation is responsible for the *in-vitro* ischaemia-induced neuronal cell death of Sprague-Dawley rats. Neurosci. lett. 387(1):22-27.
Luszczki J, Sawicka K, Kozinska J, Borowiczka K (2007). Furosemide potentiates the anticonvulsant action of valproate in the mouse maximal electroshock seizure model. Epilepsy res. 76(1):66-72.
Margineau DG, Klitgaard H (2006). Differential effects of cation-chloride co-transport blocking diuretics in a rat hippocampal slice model of epilepsy. Epilepsy Res. 69(2):93-99.
Murthy JMK (2011). Seizure aggravation with antiepileptic drugs in idiopathic generalized epilepsies. Neurology India. 59(1):51-62.
Nasser MI, Shupeng L, Kim MO (2009). Maternal epileptic seizure induced by pentylenetetrazol: apoptotic neurodegeneration and decreased $GABA_{B1}$ receptor expression in prenatal rat brain. Molecular Brain. 2: 20 doi: 10.1186/1756-6606-2-20.
Naveen KM, Gokul CG, Somashekar HS, Prabhakar A (2011). Anticonvulsant activity of flupirtine in albino mice. Pharmacol. online 3:860-867.
Palmer GC, Stagnitto ML, Ray RK, Knowles MA, Harvey R, Garske GE (1993). Anticonvulsant properties of calcium channel blockers in mice: N-methyl-D-,L-aspartate and Bay K 8644-induced convulsions are potently blocked by the dihydropyridines. Epilepsia 34(2):372-380.
Park JH, Cho H, Kim H, Kim K (2006). Repeated brief epileptic seizures by pentylenetetrazole cause neurodegeneration and promote neurogenes in discrete brain regions of freely moving adult rats. Neuroscience 140(2):673-684.
Porter RJ, Cereghino JJ, Gladding GB (1984). Antiepileptic drug development program. Cleve. Clin., 51:293-305.
Racine RJ (1972). Modification of seizure activity by electrical stimulation. II. Motor Seizure. Electroencephalography and Clinical Neurophysiol. 32(3):281-294.
Reid KH, Shang ZG, Vasudeva GI (2000). Agents which block potassium-chloride cotransport prevent sound-triggered seizures in post-ischaemic audiogenic seizure-prone rats. Brain Res. 864:134-137.
Sanchez-Gomez MV, Alberdi E, Perez-Navarro E, Alberch J, Matute C (2011). Bax and calpain mediate excitotoxic oligodendrocyte death induced by activation of both AMPA and Kainate receptors. J. Neurosci. 31(8):2996-3006.
Sankar R, Holmes GL (2004). Mechanisms of action for the commonly used antiepileptic drugs: relevance to antiepileptic drug-associated neurobehavioral adverse effects. J. Child Neurol. 19(S1):S6-14.
Srivastava AK, Gupta YK (2001). Aspirin modulates the anticonvulsive effect of diazepam and sodium valproate in pentylenetetrazole and maximal electroshock induced seizures in mice. Indian J. Physiol. Pharmacol. 45(4):475-480.
Staley KJ (2002). Diuretics as antiepileptic drugs: should we go with the flow? Review Article. Epilepsy Curr. 2(2):35-38 doi: 10. 1046/i.1535-7597.2002.00018.x
Staley KJ, Longacher M, Bains JS, Yee A (1998). Presynaptic modulation of CA3 network activity. Nat. Neurosci. 1:201-209.
Stringer JL, Pan E (1997). Effect of seizures and diuretics on the osmolality of the cerebrospinal fluid. Brain Res. 745(1-2):328-330.
Szekeres M, Nadasy GL, Turu G, Supeki K, Svidonya L, Buday L, Chaplin T, Clark A, Hunyady L (2010). Angiotensin 11-induced expression of BDNF in human and rat adrenocortical cells. Endocrinology 151(4):1695-1703.
Territo PR, Freise KJ, Newhall K, Barnhart SD, Peters SC, Engleking DR, Burnett TJ, Abdul-Karim B, Shannon HE (2007). Development and validation of the maximal electroshock seizure model in dogs. J. Vet. Pharmacol. Therap. 30(6):508-515.
Vercueil L (2004). Epilepsy and neuro-degenerative disorders in adults. Epileptic Disord. 6(1):47-57.
Weiss SA, Faber DS (2010). Field effects in the CNS play functional roles. Front. Neural Circuits 4:15.doi:10.3389.