Seizure Susceptibility and Epileptogenesis in a Rat Model of Epilepsy and Depression Co-Morbidity

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Although a strong co-morbidity exists clinically between epilepsy and depression, the cause of this co-morbidity remains unknown, and a valid animal model is crucial for the identification of underlying mechanisms and the development of a screening tool for novel therapies. Although some rodent models of epilepsy have been reported to display behaviors relevant to affective disorders, the seizure susceptibility of animals prone to depression-like behavior has not been characterized. Toward this end, we assessed several forms of seizure sensitivity and epileptogenesis in rats selectively bred for vulnerability (Swim Lo-Active; SwLo) or resilience (Swim High-Active; SwHi) to depression-like phenotypes. The SwLo rats exhibit decreased motor activity in a swim test and other depression-like phenotypes, whereas the SwHi rats display increased motor activity in a swim test. SwLo rats exhibited a decreased latency to limbic motor seizures following acute pilocarpine administration in the absence of differences in pilocarpine pharmacokinetics, and also had a decreased threshold to tonic seizures induced by electroshock. Approximately half of the SwLo rats, but none of the SwHi rats, had spontaneous limbic motor seizures 5 weeks following pilocarpine-induced status epilepticus. While the number of stimulations required to achieve full amygdala and hippocampal electrical kindling were similar in the two rat lines, SwLo rats had a lower final hippocampal kindling threshold and more wet dog shakes during both amygdala and hippocampal kindling. Combined, these results indicate that SwLo rats are a model of epilepsy and depression co-morbidity that can be used for investigating underlying neurobiological and genetic mechanisms and screening novel therapeutics.

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INTRODUCTION

A wealth of clinical data has established a strong co-morbidity between epilepsy and depression (Hesdorffer *et al*, 2006; Kanner, 2003; Kanner and Balabanov, 2002). This co-morbidity is bi-directional; that is, patients with epilepsy are three to five times more likely to develop depression, and patients with active depression, a history of depression, or a family history of depression are nearly twice as likely to develop epilepsy, a risk which rises to 4.2-fold if they have a history of suicide attempt (Hesdorffer *et al*, 2006; Morgan *et al*, 2012). Depression has a more profound impact on the quality of life of individuals with epilepsy than seizure frequency or severity (Boylan *et al*, 2004; Cramer *et al*, 2003; Jehi *et al*, 2011; Johnson *et al*, 2004; Kanner, 2006; Pulsipher

et al, 2006). Importantly, this co-morbidity is also highly detrimental to overall prognosis and outcome, as patients with both disorders exhibit higher rates of re-hospitalization and decreased success with treatment. Indeed, several antiepileptic medications, such as gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate, can cause depressed mood, whereas some antidepressants increase seizure risk, particularly in overdose situations (Hesdorffer and Kanner, 2009; Judge and Rentmeester, 2011).

Several reasons for this co-morbidity have been posited, including shared neurobiological pathways, neuroanatomical regions, and common genetic mechanisms (Harden, 2002; Kanner and Balabanov, 2002; Sankar and Mazarati, 2010; Wiegartz *et al*, 1999). The high incidence and impact of depression in epilepsy has become such a concern that an expert panel of neurologists and psychiatrists from the Epilepsy Foundation's Mood Disorders Initiative wrote and published a 'Consensus Statement' to improve the recognition and treatment of depressive disorders in patients with epilepsy (Barry *et al*, 2008), and a valid animal model is needed to identify underlying mechanisms and develop a screening tool for novel therapeutics (Jobe *et al*, 1999).

Although several studies have assessed depression-like symptoms in epilepsy-prone animals (Jobe, 2003; Jones et al, 2008; McIntyre and Gilby, 2007; Pineda et al, 2011), there is only one study in which seizure susceptibility was assessed in an animal model of depression, the Swim Lo-Active (SwLo) rats (Tabb et al, 2007), which were selectively bred for low activity in a swim test and also exhibit other depression-like and anhedonic behaviors such as decreased response to dopaminergic drugs and increased intracranial self-stimulation threshold (Weiss et al, 1998, 2008; West et al, 1999a, b; C. West, personal communication). Their counterparts, the swim High-Active (SwHi) rats, were selectively bred for high struggling activity in a swim test, and serve as a model of depression resilience (Weiss et al, 1998).

In that paper, we reported that SwLo rats have increased mortality following kainic acid-induced limbic seizures, but no differences in flurothyl-induced generalized seizure susceptibility, suggesting that the SwLo rats are specifically sensitive to limbic seizures (Tabb et al, 2007). This was of particular interest because the rate of depression is higher for patients with temporal lobe epilepsy, who suffer from recurrent limbic seizures, than other forms of epilepsy (Kondziella et al, 2007; Piazzini et al, 2001). Although these initial results in the SwLo rats were provocative, they had several major limitations; mortality rate in the 24 h following kainic acid administration was not a specific measure of seizure susceptibility in so far as we did not have direct evidence that the animals died from seizures. Also, brain levels of kainic acid were not measured and epileptogenesis was not assessed. Thus, we undertook the present studies to further investigate limbic seizure susceptibility and epileptogenesis in the SwLo rat to determine its utility as a model of epilepsy and depression co-morbidity.

MATERIALS AND METHODS

Selectively Bred Rats

SwLo and SwHi rats were selectively bred as described (Weiss et al, 1998). Two- to four-month-old rats were subjected to a 15-min swim in a tank of 25 °C water. Duration of struggling (active movement of all four paws, forepaws breaking surface of water) and floating (complete immobility, no limb movement) were measured. All experiments used male rats of generations 34–56. A subset of rats in each experiment were exposed to a swim test to confirm the persistence of this phenotype in each line, whereas the remaining littermate animals were experimentally naive. On average, SwLo rats typically float for a minimum of 600 s and struggle for no more than 10 s of a 15-min test, whereas SwHi rats float for less than 20 s and struggle in excess of 200 s (Weiss et al, 2008). No differences in seizure susceptibility were observed between the swim test-exposed and naive rats, and data were combined. Each rat was used only once in a seizure experiment, and a period of at least 1 week was given following exposure to the swim test before seizure induction. Rats were maintained on 12 h light–dark cycle, with standard rat chow and water available ad libitum. All experiments were approved by the Emory University Institutional Animal Care and Use Committee.

Pilocarpine-Induced Seizures

Rats (approximately 2–4 months of age) were injected with the peripheral muscarinic antagonist atropine methyl bromide (2 mg/kg, s.c., Sigma-Aldrich, St Louis, MO) 30 min before pilocarpine hydrochloride administration (380 mg/kg, i.p., Sigma-Aldrich, St Louis, MO). Rats were placed in a clear chamber with continuous video monitoring, and latency to limbic motor seizure, defined as bilateral forelimb clonus with rearing and falling behaviors, was measured. Rats that did not achieve a limbic motor seizure within 1 h following pilocarpine administration received a booster dose of pilocarpine (190 mg/kg).

A subset of rats from the acute pilocarpine study was allowed to sustain 1 h of status epilepticus before seizures were terminated with diazepam (5 mg/kg, i.p., Sigma-Aldrich, St Louis, MO). Five weeks later, these rats were returned to their individual test chambers and continuously video recorded during a 12-h dark cycle, and video was scored for spontaneous limbic motor seizures. During the following light cycle, rats were subjected to a 15-min swim stress, as described above. No seizures occurred during the swim test. Rats were then returned to the test chambers and continuously video recorded during the next dark cycle, and videos were again scored for spontaneous seizures. This allowed us to observe any delayed effects of stress on spontaneous seizure incidence, an important consideration given the known effects of stress on depression and epilepsy in humans (Frucht et al, 2000; Haut et al, 2003; Heim and Binder, 2012; Sperling et al, 2008).

Pilocarpine Pharmacokinetics

Rats were administered atropine and pilocarpine as described above, then euthanized 5, 10, or 15 min later. The dorsal hippocampus was dissected on ice, and tissue pilocarpine levels were measured by HPLC.

All reagents used in this assay were HPLC grade quality. Milli-Q water was used for preparation of all solutions (Millipore, Bedford, MA, USA). Pilocarpine was obtained from Sigma Chemical (St Louis, MO, USA). For the brain calibrator curve, 30 mg of control (untreated) rat brain tissue was homogenized in 0.5 ml of 0.9% saline and spiked to achieve the desired concentrations of 0, 25, 150, and 300 µg/g brain tissue. Thirty mg of unknown brain samples were weighed and homogenized in 0.5 ml saline. Brain homogenate samples and calibrators were mixed with 2 ml of dichloromethane in $16 \times 100 \, \text{mm}^2$ polypropylene test tubes. Samples were shaken for 10 min on an Eberbach shaker and then centrifuged at 2100 g in a Beckman Coulter Allegra X15R for 10 min at 23 °C. The samples were frozen in a −80 °C freezer for 10 min to facilitate separation of the two phases. The liquid organic supernatants were then transferred to $13 \times 100 \, \text{mm}^2$ glass test tubes and evaporated to dryness at 40 °C under a nitrogen stream. The residues were dissolved in 200 µl of HCl (1 mM) by vortex mixing for 1 min. The reconstituted samples were washed with 2 ml of diethyl ether by vortex mixing for 2 min and then centrifuged (2100 g, 10 min). After discarding the ether supernatant, the aqueous samples were exposed to vacuum (20 s) to remove residual ether.

The HPLC system included a Waters model 510 pump, Waters model 717 sample injector, Waters model 2487 UV detector, and a Altima C18 analytical column (5μ; $4.6 \times 150\,mm^2$). Samples were analyzed at 214 nm and the flow rate of the mobile phase was 1.2 ml/min. The mobile phase contained 35% acetonitrile and 65% of a solution of $7\,mM\;KH_2PO_4$ (pH 4.0). Drug concentrations were quantified by comparing sample peak areas against the linear regression of calibrator sample peak areas from a four-point standard curve (0, 25, 150, and 300 μg pilocarpine/g brain). The limit of detection for the assay was 5 μg/g. Pilocarpine levels were expressed in μg/g.

Increasing Current Electroshock-Induced Seizures

Electroshock seizures were induced by application of electrical stimulation via earclip electrodes using an Ugo Basile ECT Unit #57800 (Ugo Basile North America, Collegeville, PA). The initial stimulation was a 100 Hz, 5 ms square wave with an intensity of 10 mA; the intensity of successive stimulations was linearly increased by 1 mA/1 s (Kitano et al, 1996), with successive stimulations separated by 1 min. This procedure was repeated until tonic hind limb flexion was observed, allowing for the identification of a seizure current threshold for each individual rat.

Electrical Kindling

Rats were anesthetized with isoflurane and implanted with a bipolar recording and stimulating electrode in the right amygdala (2.6 mm posterior, 4.6–5.0 mm lateral, and 7.1–8.1 mm below dura, relative to bregma) or right dorsal hippocampus (3.7 mm posterior, 2.5 mm lateral, and 2.7–3.2 mm below dura, relative to Bregma; Paxinos and Watson, 1998). The electrode and a ground screw (placed over the ipsilateral cortex) were fitted into a head cap (Plastics One, Roanoke, VA) and anchored in place using dental cement.

One week following electrode implantation, two Grass S44 stimulators and two Grass PSIU6 constant current stimulus isolators (Grass Technologies, West Warwick, RI) were used to deliver a 1.0-s train of 1.0 ms biphasic rectangular pulses at 60 Hz. Electrographic seizure activity was recorded using a Grass 78D Polygraph (Grass Technologies) for the entire duration of the seizure. The initial kindling stimulation determined the seizure threshold to be used for kindling stimulations. For each rat, seizure threshold was determined by applying a starting stimulation of 50 μA. If an electrographic seizure was not induced, the stimulation was increased by 25 μA every 60 s until seizure spiking was observed. This threshold stimulation, which initially evoked an electrographic seizure but no behavioral seizure activity, was then used for all further tests of the rat. Kindling stimulations were applied twice daily (4 h inter-stimulation interval). Behavioral seizures were classified using a modified Racine scale (He et al, 2004): 0, normal activity; 1, facial clonus, immobility, wet dog shakes, and/or stiffened tail; 2, head nodding/bobbing; 3, unilateral forelimb clonus, continuous body clonus (without loss of posture); 4, rearing with bilateral forelimb clonus, severe continuous whole-body clonus; 5, rearing and falling (loss of postural control); 6, tonic-clonic seizure. In addition, the number of wet dog shakes observed during each stimulation was recorded. If at any point during the kindling stimulations a rat failed to show both electrographic seizure and seizure behaviors for two consecutive stimulations, the threshold value was redetermined, beginning with the previously defined threshold value and increasing intensity by 25 μA every 1 min until an electrographic seizure was obtained. This new threshold value was then used for all further stimulations.

A rat was considered to have reached a fully kindled state after three consecutive Class 4 or higher seizures. Stimulations were terminated in any rats that had not achieved kindled status by 40 stimulations in the amygdala or 80 stimulations in the hippocampus. At the conclusion of the kindling experiment, proper electrode placement was confirmed by cresyl violet staining.

Statistical Analysis

Data were analyzed using a Student's t-test for the acute pilocarpine, increasing current electroshock, and kindling studies, a two-way ANOVA for the pilocarpine pharmacokinetics, and a Fisher's Exact Test for the chronic pilocarpine experiments. All data analysis was conducted using Prism GraphPad 5.0 and IBM SPSS 17.0.

RESULTS

Acute Pilocarpine-Induced Seizure Susceptibility

Following acute administration of pilocarpine (380 mg/kg, i.p.), SwLo rats displayed a decreased latency to limbic motor seizure compared with SwHi rats ($t_{20} = 3.528$, $p < 0.01$; Figure 1a).

Pilocarpine Pharmacokinetics

To verify that the increased pilocarpine-induced seizure susceptibility in the SwLo rats was not due to a difference in the concentration of pilocarpine present in the brain (ie, differences in pilocarpine pharmacokinetics), hippocampal tissue samples were analyzed for pilocarpine levels 5, 10, and 15 min following administration of pilocarpine (380 mg/kg, i.p.). Brain pilocarpine levels increased over time in both SwLo and SwHi rats, but no differences between lines were observed (Figure 1b). Two-way ANOVA revealed a significant effect of time ($F_{2,12} = 8.13$, $p < 0.01$) but not line ($F_{1,12} = 0.07$, $p = 0.80$) or time x line interaction ($F_{2,12} = 0.63$, $p = 0.55$).

Increasing Current Electroshock Seizures

To assess whether differences in seizure susceptibility were restricted to chemoconvulsant-induced seizures, we tested SwLo and SwHi rats in an increasing current electroshock seizure paradigm. As shown in Figure 2, SwLo rats seized at a lower electroshock threshold than SwHi rats, ($t_{10} = 9.391$, $p < 0.0001$).

Pilocarpine-Induced Spontaneous Seizures

Five weeks following a 1 h period of status epilepticus induced by pilocarpine (380 mg/kg, i.p.), SwLo and SwHi rats were video recorded and assessed for the appearance of
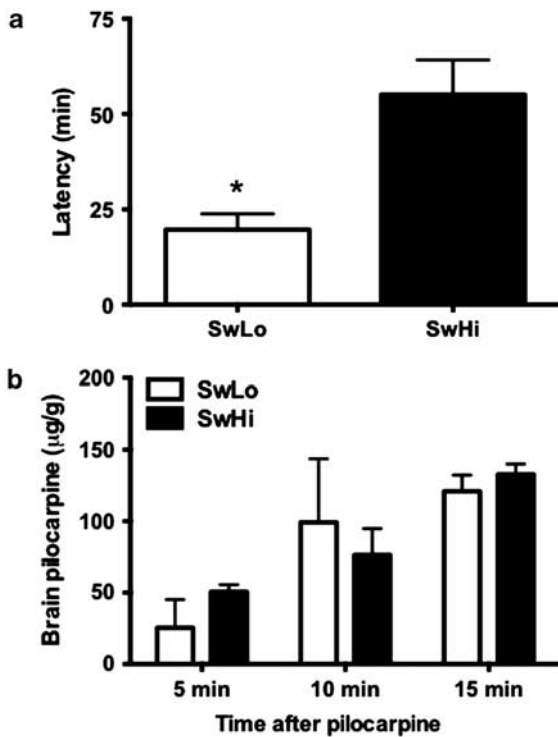
Figure 1 SwLo rats have a shorter latency to pilocarpine-induced seizures than SwHi rats that is independent of pilocarpine pharmacokinetics. (a) SwLo ($n=11$) and SwHi ($n=11$) rats were injected with atropine methyl bromide (2 mg/kg, i.p.), followed by pilocarpine (380 mg/kg, i.p.) 30 min later, and latency (mean ± SEM) to limbic motor seizures was measured. *$p<0.01$ compared with SwHi rats. (b) SwLo ($n=3$) and SwHi ($n=3$) rats were treated with atropine and pilocarpine as above, euthanized 5, 10, or 15 min later, and hippocampal pilocarpine levels (mean ± SEM) were measured by HPLC.
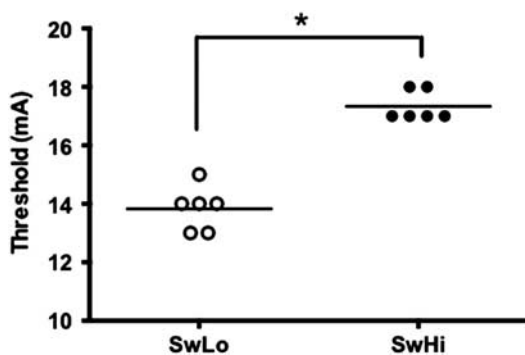

Figure 2 SwLo rats are more susceptible to electrically induced seizures than SwHi rats. Increasing current was delivered via earclip electrodes to SwLo and SwHi rats ($n=6$ per group), and threshold stimulation required to induce tonic hind limb flexion was recorded. *$p<0.0001$.

spontaneous limbic seizures during the dark cycle. Approximately 25% (2/9) of the SwLo rats had spontaneous seizures, whereas none of the SwHi rats did. The next day, rats were subjected to a 15-min swim stress during the light cycle, and again assessed for spontaneous seizures during the following 12-h dark cycle. Both of the SwLo rats that had spontaneous seizures the previous night, plus two addi-

tional SwLo rats, had spontaneous seizures, for a total of 4/9 (44%), whereas none of the SwHi rats had spontaneous seizures. This difference did not achieve statistical significance ($p=0.10$).

Electrical Kindling

SwLo and SwHi rats did not differ in initial stimulation threshold for the amygdala or hippocampus (Figure 3a and b). Although amygdala kindling threshold did not change over time for either line, 4/9 SwHi rats required an increase in threshold to achieve electrographic seizures during hippocampal kindling, whereas none of the SwLo rats did, resulting in a significant difference in final threshold stimulation level between rat lines (Figure 3b). A two-way repeated-measures ANOVA revealed a main effect of line ($F_{1,17}=5.915$, p=0.0264), initial *vs* final time point ($F_{1,17}=6.066$, $p=0.0248$), and a line x time point interaction ($F_{1,17}=6.066$, $p=0.0248$). Bonferroni's *post-hoc* tests showed a significant difference between the initial and final threshold value in SwHi rats ($t_{17}=3.395$, $p<0.01$) and between final threshold values of SwHi and SwLo rats ($t_{17}=2.959$, $p<0.05$). Furthermore, SwLo rats showed more wet dog shakes during both amygdala and hippocampal kindling ($t_{281}=5.526$, $p<0.0001$ for amygdala, $t_{1214}=8.004$, $p<0.0001$ for hippocampus; Figure 3c and d). There were no significant differences between SwLo and SwHi rats in the rate of progression to any seizure stage, including the number of stimulations required to reach a fully kindled state, for the amygdala or hippocampus (Figure 3e and f).

DISCUSSION

The results presented here support the validity of SwLo rats as an animal model of epilepsy and depression co-morbidity. The depression-like phenotypes of SwLo rats (ie, low activity in the forced swim test that is reversible by chronic but not acute antidepressant treatment, decreased response to dopaminergic drugs (Weiss *et al*, 1998; Weiss *et al*, 2008; West *et al*, 1999a, b; West and Weiss, 1998)) have been described previously. Here, we show that SwLo rats have increased acute susceptibility to seizures induced by chemoconvulsants and electroshock, and also show exacerbated epileptogenesis in the chronic pilocarpine model and certain parameters of electrical kindling.

Seizure Susceptibility and Epileptogenesis in the SwLo Rat

We reported before that SwLo rats had a higher incidence of mortality following kainic acid-induced limbic seizures but no differences in generalized flurothyl-induced tonic-clonic seizure susceptibility, suggesting that SwLo rats might be particularly prone to limbic seizures (Tabb *et al*, 2007). This distinction is of interest because there is evidence to suggest that temporal lobe epilepsy has an increased association with depression compared with other forms of epilepsy (Kondziella *et al*, 2007; Piazzini *et al*, 2001). Our present results appear to partially support this idea, as SwLo rats are also more sensitive to acute limbic seizures induced by pilocarpine, as well as spontaneous limbic seizures in the
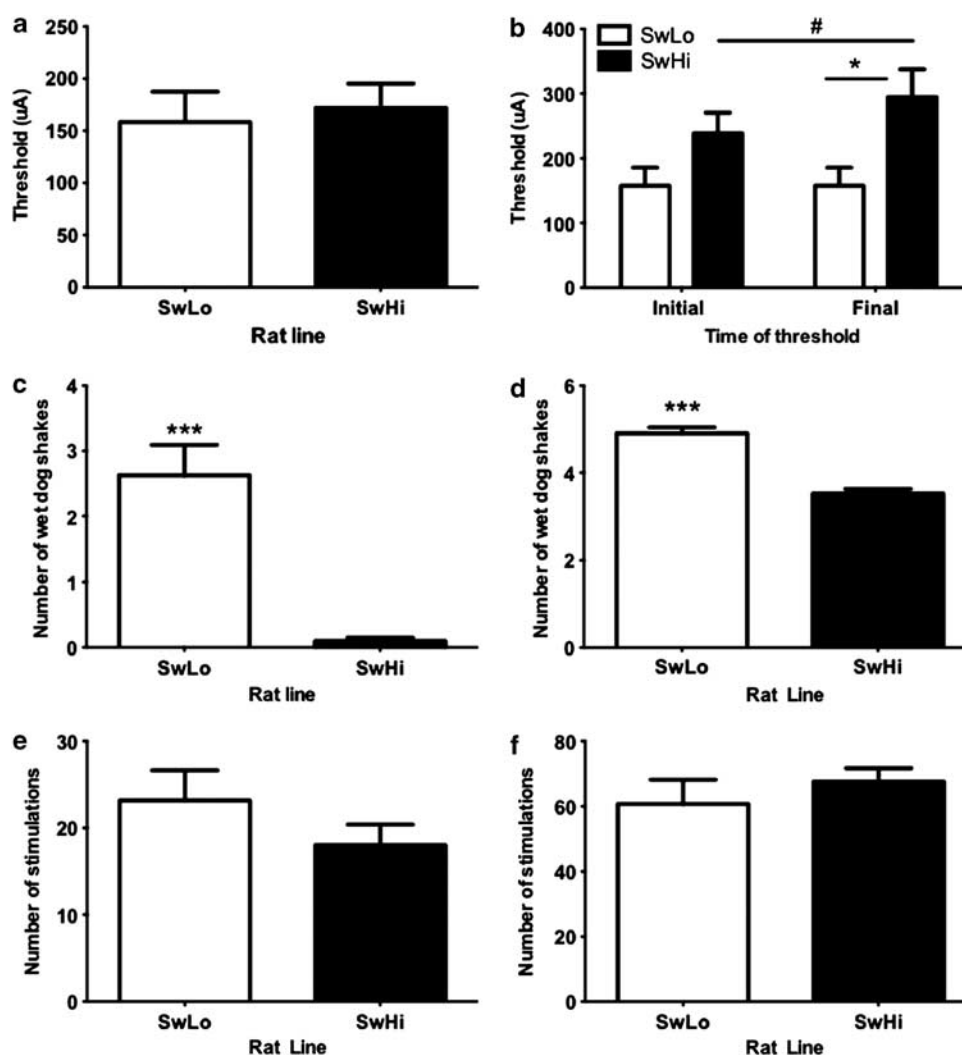
Figure 3 Kindling parameters in SwLo and SwHi rats. SwLo and SwHi rats ($n = 6$–10 per group) were implanted with electrodes in the amygdala or hippocampus. Initial electrographic seizure threshold was determined, and threshold stimulations were delivered twice per day until rats reached a fully kindled state, defined as three consecutive rearing/falling seizures. Shown are the mean ± SEM of initial and final threshold used to induce an electrographic seizure during amygdala (a) and hippocampal (b) kindling, the number of wet dog shakes during amygdala (c) and hippocampal (d) kindling, and the number of stimulations required to reach a fully kindled state in the amygdala (e) and hippocampus (f). $*p < 0.05$, $***p < 0.0001$ compared with SwHi rats, $^{\#}p < 0.01$ compared with initial threshold for that rat line.

weeks following pilocarpine-induced status epilepticus. However, this association is complex, and this is an area of ongoing study and debate (Hoppe and Elger, 2011). Rates of depression are also elevated in patients with non-limbic generalized epilepsies, suggesting that structures outside of the temporal lobe may also be implicated in the co-morbidity. This may be true in our model, as SwLo rats had a lower threshold for electroshock-induced tonic seizures, which likely also involve brainstem structures (Shehab et al, 1995).

The appearance of spontaneous seizures in the weeks following pilocarpine-induced status epilepticus in SwLo rats, although not statistically significant, is an important extension of our previous findings. The presence of spontaneous seizures in nearly half of the SwLo rats, but in none of the SwHi rats, suggests increased epileptogenesis in addition to the acute differences in seizure susceptibility. This enhanced epileptogenesis is also more relevant to the

clinical evidence supporting a co-morbidity between depression and the development of epilepsy itself, not just increased seizure susceptibility.

Given the importance of the amygdala and hippocampus in both limbic seizures and depression, we suspected that electrical kindling would be accelerated in these brain regions in SwLo rats. Although we did not find this epileptogenic criterion to be altered in the SwLo rats, we did observe an increased incidence of wet dog shakes during kindling. Furthermore, many of the SwHi rats required an increase in stimulation magnitude to achieve threshold for electrographic seizures during the kindling process, whereas none of the SwLo rats did. Bragin et al (2002) reported a similar threshold increase during kindling in rats that had been previously treated with an intrahippocampal injection of kainic acid. They interpreted this phenomenon as a compensatory protective response to seizure generation and propagation, consistent with

evidence that a variety of compensatory cellular and molecular changes occur in the epileptic brain (McNamara, 1994). If the same processes account for the increased threshold in both the intrahippocampal kainic acid and electrical kindling paradigms, this would suggest that SwLo rats lack this adaptive protective capacity. It is also possible that SwHi rats have an inherently seizure-resistant brain, which is consistent with our finding that none of the SwHi rats developed spontaneous seizures following pilocarpine-induced status epilepticus, even following a swim stress that increased the incidence of spontaneous seizures in the SwLo line.

Potential Mechanisms Underlying the SwLo Seizure Phenotypes

Genetic risk factors contribute significantly to epilepsy, depression, and the interaction between these diseases. For example, over 50% of epileptic patients with depression have a family history of psychiatric illness (Kanner and Nieto, 1999; Robertson et al, 1987). One advantage of the SwLo rats as a model of epilepsy and depression co-morbidity is that these animals have been selectively bred for over 50 generations and are genetically homogenous (Weinshenker et al, 2005; unpublished data). Furthermore, cross-fostering experiments with SwHi rats have revealed that the SwLo swim test phenotype is heritable and controlled by the genotype of the offspring rather than being due to potential differences in rearing (unpublished data and C. West, personal communication). Thus, mapping and identifying genes controlling depression-like behavior and seizure susceptibility differences between SwLo and SwHi rats is possible using quantitative trait loci analysis. Although quantitative trait loci and other linkage analyses have been used to map and identify risk factor genes for epilepsy or depression separately, the SwLo and SwHi rats seem to represent an excellent tool for the discovery of co-morbidity genes.

It is not clear a priori what types of genes underlie the SwLo phenotypes, but we speculate that noradrenergic dysfunction could be an important contributor. A large body of evidence indicates that norepinephrine has potent antic-onvulsant and antiepileptogenic properties (Giorgi et al, 2006; Giorgi et al, 2004; Kokaia et al, 1989; Seo et al, 2000; Stanton, 1992; Szot et al, 1999; Weinshenker and Szot, 2002). For example, norepinephrine depletion accelerates the development of hippocampal kindling and increases carba-chol-induced wet dog shakes in rats, whereas central injection of norepinephrine decreases wet dog shakes (Ferencz et al, 2001; Kokaia et al, 1989; Turski et al, 1982; but see Bortolotto and Cavalheiro, 1986). These findings are of particular interest because SwLo rats have a selective decrease of norepinephrine in the hippocampus (Weiss et al, 2008), and chronic administration of norepinephrine reup-take inhibitors reverses depression-like phenotypes in SwLo rats in the swim test (Weiss et al, 1998; West and Weiss, 1998). Cholinergic dysfunction is another potential culprit. For example, we have shown in this study that SwLo rats are more susceptible to seizures and epileptogenesis induced by the muscarinic acetylcholine receptor agonist, pilocarpine. SwLo rats also have a higher incidence of wet dog shakes during kindling, and disturbances in the muscarinic system

have been implicated in wet dog shakes induced by carbachol (Turski et al, 1984). These noradrenergic and cholinergic associations need to be tested empirically, and other neurotransmitter systems that modulate both mood and neuronal excitability (eg, serotonin, neuropeptides) could also be involved.

Conclusion

Although multiple studies have been conducted assessing depression-like phenotypes in rodent models of epilepsy, the SwLo rats are, to our knowledge, the only example of animals selected and developed specifically for depression-related behavior that also show phenotypes relevant to epilepsy. Thus, the SwLo rats represent a unique model for identifying the genes and mechanisms underlying co-morbid depression and epilepsy, as well as a preclinical tool to screen novel therapeutics for safety and efficacy in treating both diseases simultaneously. Although the focus of this study was on the SwLo rats as a model for susceptibility to epilepsy and depression, the SwHi rats are also of interest. Because the depression- and epilepsy-like phenotypes of 'wild-type', non-selected rats tend to fall somewhere in between those of SwLo and SwHi rats (Tabb et al, 2007; Weiss et al, 1998; Weiss et al, 2008; unpublished data), the SwHi rats may be a model for co-morbidity resilience.

DISCLOSURE

The authors declare no conflict of interest.

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