



# Repeatedly stressed rats have enhanced vulnerability to amygdala kindling epileptogenesis

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**Summary** Psychiatric disorders associated with elevated stress levels, such as depression, are present in many epilepsy patients, including those with mesial Temporal Lobe Epilepsy (mTLE). Evidence suggests that these psychiatric disorders can predate the onset of epilepsy, suggesting a causal/contributory role. Prolonged exposure to elevated corticosterone, used as a model of chronic stress/depression, accelerates limbic epileptogenesis in the amygdala kindling model. The current study examined whether exposure to repeated stress could similarly accelerate experimental epileptogenesis. Female adult non-epileptic Wistar rats were implanted with a bipolar electrode into the left amygdala, and were randomly assigned into stressed ( $n = 18$ ) or non-stressed ( $n = 19$ ) groups. Rats underwent conventional amygdala kindling (two electrical stimulations per day) until 5 Class V seizures had been experienced ('the fully kindled state'). Stressed rats were exposed to 30 min restraint immediately prior to each kindling stimulation, whereas non-stressed rats received control handling. Restraint stress increased circulating corticosterone levels (pre-stress:  $122 \pm 17$  ng/ml; post-stress:  $632 \pm 33$  ng/ml), with no habituation observed over the experiment. Stressed rats reached the 'fully kindled state' in significantly fewer stimulations than non-stressed rats ( $21 \pm 1$  vs  $33 \pm 3$  stimulations;  $p = 0.022$ ; ANOVA), indicative of a vulnerability to epileptogenesis. Further, seizure durations were significantly longer in stressed rats ( $p < 0.001$ ; ANOVA). These data demonstrate that exposure to repeated experimental stress accelerates the development of limbic epileptogenesis, an effect which may be related to elevated corticosterone levels. This may have implications for understanding the effects of chronic stress and depression in disease onset and progression of mTLE in humans.

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## 1. Introduction

Many patients with epilepsy suffer from major psychiatric comorbidities, including depression, anxiety, psychoses, cognitive disorders and increased suicidal ideation and attempts (Tellez-Zenteno et al., 2007; Hermann et al., 2008). Although many clinicians associate this particularly with mesial Temporal Lobe Epilepsy (mTLE), recent studies have demonstrated that patients with other focal and generalised epilepsy syndromes are similarly affected (Christensen et al., 2007; Adams et al., 2008; Hermann et al., 2008). The increased prevalence of these psychiatric disturbances has been variously attributed to the psychosocial consequences of living with a neurological disorder, to long-term medication effects, to the repeated damaging effects of seizures on the brain, or to a common underlying neurobiological abnormality (Jobe, 2003; Kanner, 2006), explanations which are not mutually exclusive. Of note, several animal models of epilepsy show a range of striking behavioural changes relevant to the psychiatric comorbidities seen in humans with epilepsy, including interictal alterations in anxiety states, depressive-like behaviours and endophenotypes of psychosis (Adamec and Young, 2000; Kalynchuk, 2000; McIntyre et al., 2002; Jobe and Browning, 2007; Mazarati et al., 2007; Jones et al., 2008, 2009, 2010; Mazarati et al., 2009), suggesting that there is at least some biological component to these comorbidities. Interestingly, in many of these models, the “psychiatric” phenotype manifests before the development of the epilepsy, opening up the possibility that this may confer an enhanced vulnerability to epileptogenesis.

Recent clinical and epidemiological research also provides support for such a bidirectional relationship between epilepsy and psychiatric disorders, where epilepsy can both predispose to the development of psychopathologies but also, conversely, be exacerbated by pre-existing or comorbid neuropsychiatric disorders (Kanner, 2011). For example, evidence exists that in some cases, psychiatric disorders can pre-date the first seizure (Forsgren and Nystrom, 1990; Hesdorffer et al., 2000, 2006) suggesting that depression and other stress-related illnesses may, in certain instances, act as risk factors for the onset of epilepsy. In addition, a lifetime history of depression preceding the onset of epilepsy (Hitiris et al., 2007), or more severe psychopathology at presentation (Petrovski et al., 2010), has been shown to be predictive of poorer seizure control with medical treatment, and also following epilepsy surgery for drug-resistant epilepsy (Kanner et al., 2009). Also, stress – heavily associated with psychiatric illnesses – is frequently reported by patients as a seizure precipitant (Frucht et al., 2000; Nakken et al., 2005).

Several recent experimental studies have investigated the effects of stress or stress mediators on the development of epilepsy, i.e. epileptogenesis. Supplementation with corticosterone, the hormonal endpoint of the Hypothalamic–Pituitary–Adrenal (HPA) axis in rodents, by adding it to the drinking water of rats (Taher et al., 2005; Kumar et al., 2007) or by implantation of a corticosterone-releasing pellet (Karst et al., 1999), enhances epileptogenesis in the amygdala kindling model of limbic epileptogenesis. A subsequent study demonstrated that this effect was mediated, at least in part, by both mineralocorticoid and glucocorticoid

receptors (Kumar et al., 2007). Conversely, retarded kindling rates have been demonstrated in adrenalectomised rats compared to rats with corticosterone replacement (Edwards et al., 1999) or with sham-operated controls (Weiss et al., 1993). Other stress mediators, in particular Corticotrophin Releasing Hormone (CRH), can induce seizures when injected in very high doses intracerebroventricularly in rats (Baram and Hatalski, 1998), and, when given repeatedly, can accelerate the rate of both electrical amygdala (Weiss et al., 1986) and chemical (cocaine) kindling (Weiss et al., 1992). Additionally, early life stress, which is recognised to upregulate HPA axis responses to stress, imparts an enduring vulnerability to experimental limbic epileptogenesis (Salzberg et al., 2007; Jones et al., 2009; Kumar et al., 2011). Although no evidence exists to suggest that stress by itself can cause epilepsy, these clinical and experimental data present a rationale that stress and stress-related disorders may enhance the vulnerability of the brain to epileptogenesis following a precipitating insult, and potentially exacerbate the disease course in established cases.

The current study aims to extend this line of research to determine whether exposure to repeated episodes of restraint stress influences limbic epileptogenesis in the amygdala kindling rat model. This study advances on previous research, which investigated the effects of administering or antagonising stress mediators, to examine the effect of a stressor itself. Repeated restraint stress is a well-established experimental intervention which activates the entire HPA axis (Marti et al., 2001), and is therefore a more accurate representation of the effect of stress in humans compared to approaches such as the supplementation of selected stress mediators.

## 2. Methods and materials

### 2.1. Animals

Female Wistar rats (total  $n = 37$ ; 200–220 g) were bred and group-housed (2–3 per cage) in the Department of Medicine (Royal Melbourne Hospital), University of Melbourne Biological Research Facility. The facility was kept on a 12 h light/dark cycle, with lights on at 0600 h, and food (standard rat chow) and water available to animals *ad libitum*. At all times, care was taken to minimise pain and discomfort of the animals, and all experimental procedures were approved by the University of Melbourne Animal Ethics Committee (#0701720).

### 2.2. Electrode implantation surgery

The implantation of bipolar electrodes into the amygdala has been previously described (Salzberg et al., 2007). Briefly, at 7 weeks of age, rats were anaesthetised by inhalation of isoflurane (5% induction, 1.5–2.5% maintenance) and positioned in a stereotaxic frame. The skull was exposed via a single midline incision along the scalp, and five holes drilled into the skull. Three gold ‘male’ connector electrodes (Farnell In One, Chester Hill, Australia) previously soldered onto nickel alloy jewellers’ screws, and one jewellers’ screw were screwed into the holes to serve as ground reference electrodes and anchoring, respectively. A

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