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Research report

Anxiolytic and anxiogenic effects of kindling—role of baseline anxiety and anatomical location of the kindling electrode in response to kindling of the right and left basolateral amygdala

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Abstract

Effects of kindling of right and left basolateral amygdala (BLA) on plus maze anxiety was studied. Using a validated retest paradigm, it was possible to retest rats in the plus maze without increasing anxiety on retest. This permitted determining prekindling baseline levels of plus maze anxiety. Right BLA kindling of high baseline anxiety rats was anxiolytic one week after kindling. Right BLA kindling of low baseline anxiety rats was anxiogenic. In addition, left BLA kindling was either anxiogenic or without effect on plus maze anxiety, depending on baseline anxiety. Effects in left BLA differ from previous work showing anxiolytic effects of left BLA kindling. The discrepancy could be explained in part by prekindling baseline anxiety. These findings require modification of the previous conclusion that left hemisphere (left BLA) kindling is anxiolytic and right BLA kindling is anxiogenic in the plus maze. Rather the hemisphere difference may be due to an interaction between baseline anxiety level and kindling. If true, anxious disposition in rodents may interact with amygdala kindling to change amygdala function differently. Kindling and baseline anxiety effects on other behaviors (such as risk assessment and resistance to capture) are also described. Present data in the light of past studies suggest both premorbid anxiety state and location of the kindling electrode contribute to the effects of kindling on behavior.

Keywords: Anxiety; Basolateral amygdala; Baseline anxiety; Body weight; Elevated plus maze; Hemisphere; Kindling; Rat; Risk assessment; Repeated testing

1. Introduction

A variety of factors impact on affect in human epileptics, including psychosocial factors, medication, premorbid psychiatric condition, family history and pathophysiology of the disorder. For these reasons it is difficult to determine the contribution of pathophysiology of the epilepsy to affective changes [8]. Given that the most commonly agreed upon forms of affective psychopathology accompanying seizure disorders in humans are depression and anxiety [8,21], it is of interest to better understand how seizures might alter emotional functioning interictally. If seizures predispose a patient to affective disorder, then one would expect that lasting changes in affect should be produced in animal models of epilepsy. This is the case, but the nature of behavioral change produced by experimental epilepsy is complicated by a number of factors.

Repeated evocation of seizures in limbic areas (limbic kindling) produces lasting changes in animal behavior, including cognition [15,30,32,39,40] and affect [1,7,11,20,23–26,28,38,42]. Moreover, kindling may increase or decrease anxiety in rodents [2,12,20].

Study of the effects of kindling on behavior have predominantly used two types of kindling, short-term and long-term kindling. Short-term kindling refers to kindling rats to three to four stage 5 seizures [2] according to the Racine [36] scale. In most studies of short-term kindling, the hole board and elevated plus maze have been used to assess rodent affect. Nevertheless effects of short-term kindling on acoustic star-

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tle [38] have been tested. In one study involving 15 stage five seizures in the right posterior BLA, rats responses in plus maze, social interaction, sucrose preference and forced swim tests were examined. Kindling lastingly increased anxiety in the plus maze and social interaction tests with no effects on the sucrose preference or forced swim tests [20]. Long-term kindling involves 60–90 stage 5 seizures, and has been shown to increase rodent defensiveness in a variety of behavioral measures [27].

Several factors contribute to the different effects of kindling on anxiety in rodents. Hemisphere of the kindling electrode is one. Kindling of the left basolateral and left central amygdala nuclei appears to be anxiolytic [12,25]. Kindling of most of the right basolateral amygdala (BLA) is anxiogenic [2,12,20]. Nevertheless, anxiolytic effects of kindling of mid locations in the right BLA have been reported [13]. These latter data point to the importance of location of the kindling electrode within a nucleus in the same hemisphere for behavioral outcome. Other examples include the findings that kindling of right anterior corticomedial amygdala nuclei is anxiogenic, whereas kindling of more posterior areas is either behaviorally neutral (medial amygdala) or anxiolytic (cortical nuclei) [2,11,12]. The reverse appears to be the case for kindling of the right central nucleus of the amygdala [5].

Another factor contributing to effect of kindling on affect is premorbid affective state. This factor is of obvious clinical significance, and may help to explain some of the discrepancies in findings of effects of kindling on rodent affect. Adamec and Shallow [4] used a novel retest paradigm with the elevated plus maze to assess levels of anxiety prior to kindling of the medial amygdala. They showed that testing rats in different novel rooms in different plus mazes with an inter test interval of three weeks prevented the apparent increase in anxiety reported with repeated testing in the plus maze [17]. In this study anxiety was measured using a common pharmacologically validated measure called ratio time [16]. This is the ratio of time spent in the open arms to time spent in all arms. The smaller this ratio, the more “anxious” the rat. Adamec and Shallow divided their rats into those with greater or lesser ratio times on the first of two tests prior to kindling but after electrode implantation. Wistar rats were implanted with electrodes in the anterior medial amygdala. Kindling electrode locations were carefully chosen to match those where kindling was shown to be anxiogenic in the elevated plus maze by Adamec and Morgan [12]. It was found that kindling was anxiogenic (reduced ratio time) only in rats with higher pre-kindling ratio time baselines. The lack of effect of kindling in rats with lower baseline ratio times was not a floor effect. In fact there was a non-significant trend for rats with lower prekindling ratio times to explore the open arms more than controls after kindling (an anxiolytic effect). One wonders if the baseline ratio times had been lower if the effects of kindling might have been anxiolytic, significantly raising ratio time. These data suggest that premorbid anxiety state interacts with amygdala kindling to determine behavioral outcome, and that the outcome may be either anxiogenic, anxiolytic or no effect at all depending on the level of anxiety at the time of kindling.

This conclusion must be tentative. Adamec and Shallow [4] only showed that effects of kindling were either neutral or anxiogenic, with the suggestion that they might also be anxiolytic if baseline conditions had been more extreme. The second is that the interaction of premorbid baseline with kindling has so far only been studied in the anterior medial amygdala.

Therefore, the present study was designed to extend to other amygdala areas the tests of the interaction of premorbid anxiety baseline with behavioral outcome of short-term kindling in the right and left BLA on anxiety like behavior assessed in the hole board and plus maze tests. Though kindling has been shown to influence anxiety like behavior in a variety of test, we chose to concentrate on the hole board and elevated plus maze tests with an eye to replicating the methods of Adamec and Shallow [4].

2. Methods: Experiment 1—kindling of the right basolateral amygdala

2.1. Subjects

Subjects were 54 male Wistar rats (Charles River Canada) weighing between 200 and 250 g at the start of the experiment. Rats were housed singly in transparent plastic cages on racks holding 15 rats. Light cycle was 12 h with lights on at 07:00 h. Water and rat chow were continuously available.

2.2. Experimental groups

Rats were adapted to the laboratory for three days before surgery as described elsewhere [12] and randomly assigned to one of three experimental groups. One group was a handled control ($n = 18$) in which rats were handled as other groups without electrode implantation. This group controlled for the effects of implanting electrodes on behavior. Previous work suggested that damage of electrode implantation in some amygdala nuclei impacted rodent anxiety [11,12]. A second control group was an implanted control ($n = 18$). These animals had electrodes implanted in the right BLA, but were not stimulated. The third group was the kindled group ($n = 18$). These rats had electrodes implanted in the right BLA and were kindled. The final number in the kindled group was reduced by one ($n = 17$) because the electrode was outside of the target area.

2.3. Surgical procedures

Surgery was performed under sodium pentobarbital anaesthesia (60 mg/kg, i.p.) using aseptic technique as described elsewhere [12]. One week of recovery from surgery was allowed before testing began.

2.4. Behavioral testing—hole board and elevated plus maze, apparatus, testing procedure

The hole board and elevated plus maze were used to test rodent anxiety. The hole board test provides an independent measure of exploration and activity [18]. The elevated plus maze is a well-known, pharmacologically validated test of rodent anxiety. The plus