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BRAIN RESEARCH

Research Report

Assessment of anxiety-like behaviors in female rats bred for differences in kindling susceptibility and amygdala excitability

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ABSTRACT

Two rat lines bred for kindling susceptibility were previously observed to engage in different behavioral strategies in tests of emotionality. In order to extend past research on defensive behaviors in these strains which largely used males, Fast- and Slow-kindling females were assessed for anxiety-like behaviors in a number of aversive paradigms. Fast rats entered and spent more time in the open arms and spent less time in the closed arms of the elevated plus-maze (EPM) compared to Slow animals. Fast rats had higher conditioned suppression ratios across testing days, defecated less often during conditioning, and successfully disinhibited suppression during extinction in the conditioned emotional response (CER) paradigm compared to Slow-kindlers. In order to pursue these differences in emotional reactivity between the strains and differentiate negative affect from motivational, learning, and impulsive explanations, a separate group of animals were assessed in the light-enhanced acoustic startle chamber, a test of anxiety. When initially exposed to a bright-light, Slow rats significantly increased their startle response while this was not observed in the Fast strain. In combination with previous research on these strains, the present data tentatively suggest that Fast and Slow animals utilize different neural systems in tests of fear and anxiety which may have been co-selected with the direct selection of amygdala-kindling susceptibility.

1. Introduction

Phenotypic variability is employed to genetically select for high/low divergent rodent lines on a trait in order to model and enhance the understanding of the genetic and neural mechanisms underlying individual susceptibility and resiliency to human neuropathology. In developing contrasting strains, individuals are selected based on upper and lower scores for a phenotype in the founder population and subsequent generations (i.e., truncated selection). This occurs in combination with repeated matings of rodents who share a targeted response to selection so that successive progeny become increasingly segregated into two strains that express either upper or lower levels of a phenotype (Koch and Britton, 2005).

Fear and anxiety are neuro-adaptive responses that allow an organism to escape or avoid a dangerous or potentially threatening situation. A number of rat lines have been intentionally selected on measures of emotionality such as defecation in the open field (Maudsley reactive and non-reactive lines; Broadhurst, 1975); learning in the two-way active avoidance task (Roman high avoidance and low avoidance; Bignami, 1965); performance in the runway test

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(Tsukuba high and low emotionality; Fujita et al., 1994); elevated plus-maze (EPM) behavior (High and Low anxiety-like behavior strains; Landgraf and Wigger, 2002); and approachability to humans (tameness and aggressive defence strains; Naumenko et al., 1989). In addition, it is often observed that bi-directionally selected strains concomitantly vary in defensive responses even though these behavioral phenotypes were not under direct selection (Anisman et al., 2008; Ballaz et al., 2007; Dess and Minor, 1996; Overstreet et al., 1997). The kindling-prone (Fast) and kindling-resistant (Slow) strains were developed by artificially selecting for amygdala-kindling susceptibility over 11 generations resulting in Fast rats requiring 20–40% fewer stimulations to kindle while the Slow animals necessitated 200–300% more stimulations compared to outbred controls (Racine et al., 1999). Although the criterion on which these strains were selected was kindling rates we found that they also displayed, possibly due to pleiotropic effects and genetic linking (DeFries, 1969), divergences in cocaine sensitivity, attention, play, impulsivity, and learning (Anisman and McIntyre, 2002; McIntyre and Gilby, 2007; McIntyre et al., 2004; Reinhart et al., 2004; Shi et al., 1999). Similarly, differences in emotionality have been observed between these strains depending on the testing paradigm employed. Fast males tend to be less fearful in the EPM, open field, and active and inhibitory avoidance tasks yet these same animals show increased struggling when restrained, whereas Slow animals adopt an immobile profile. When exposed to a ferret, Fast rats are less ambulatory compared to Slow rats and although the Slow-kindlers express a higher baseline acoustic startle, Fast-kindlers produce a fear-potentiated reflex where no such response is detected in Slow animals. Furthermore, when tested for sucrose consumption in a novel environment, Fast rats had no alteration in their intake relative to their familiar home cage but the Slow rats consumed significantly less sucrose in the unfamiliar environment and this reduction was eliminated with diazepam (Anisman et al., 1997; Kelly et al., 2003; McIntyre et al., 1999; Mohapel and McIntyre, 1998).

In humans women are more likely to be affected by mood disorders (Kessler et al., 1994) and in animal studies on negative affect males tend to be over-represented (Palanza, 2001; Wintink et al., 2003). For this reason, it was of interest to extend our understanding of emotional responding in the Fast and Slow strains to females. Fast and Slow females were first assessed in the EPM and open field, tests in which male rats of these strains were previously examined in (Mohapel and McIntyre, 1998). Since these lines were selected for amygdala-kindling susceptibility it is likely that the strain differences in fear behaviors stem from the amygdala and its associated networks because this structure mediates responses to aversive events (Goddard, 1964; Hubbard et al., 2007; Kapp et al., 1991; Koo et al., 2004; LeDoux, 2003; Yang et al., 2006). As a result, we additionally placed female rats in the conditioned emotional response (CER) and light-enhanced acoustic startle paradigms which are known to rely on amygdala activation (Davis, 1990; Walker and Davis, 1997a, 1997b) and have been pharmacologically validated by anxiolytics (de Jongh et al., 2002; Méthot and Deutsch, 1984; Stanhope and Dourish, 1996; Walker and Davis, 2002).

2. Results

Unpaired *t*-tests revealed a significant difference for closed arm entries [$t(18)=3.34$; $p<.01$; Fig. 1A] in the EPM with Fast rats making more closed arm entries than Slow rats. Similarly, Slow animals spent more percent time in the closed arms [$t(18)=2.44$; $p<.05$; Fig. 1B] than did the Fast rats. For open arm behaviors Fast rats significantly made more open arm entries [$t(18)=3.53$; $p<.01$; Fig. 2C] than Slow

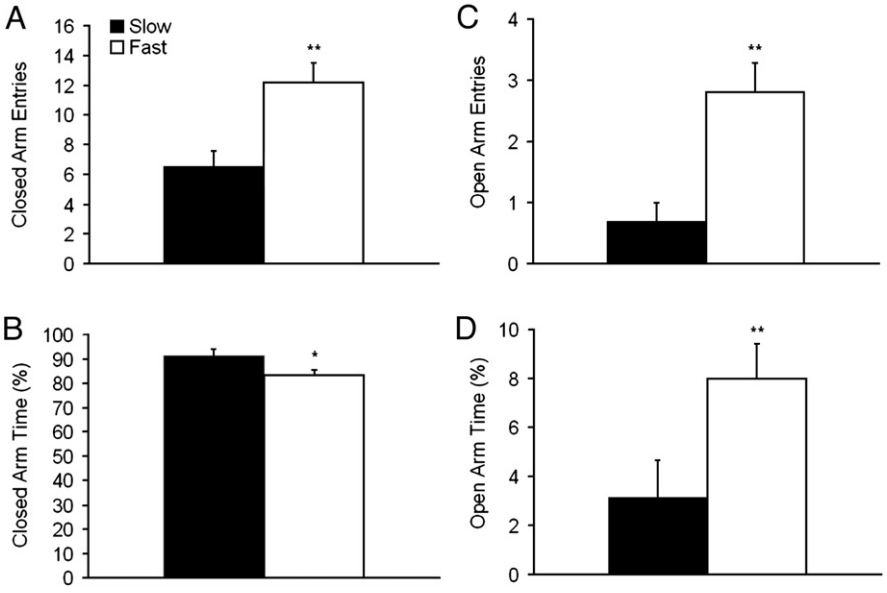

Fig. 1 – Mean (±S.E.M.) scores in EPM for Fast and Slow females. (A) Number of closed arm entries; (B) Percent number of seconds spent in closed arms of total EPM time; (C) Number of open arm entries; (D) Percent time in seconds spent in open arms of total EPM time. *$p<.05$; **$p<.01$.