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BRAIN RESEARCH

Research Report

The NMDA receptor antagonist CPP blocks the effects of predator stress on pCREB in brain regions involved in fearful and anxious behavior

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ABSTRACT

A 5-min unprotected exposure to a cat produces long-lasting anxiogenic effects on behavior which are NMDA receptor-dependent. Since phosphorylation of CREB is regulated by NMDA receptors and pCREB-like-immunoreactivity (lir) is increased after predator stress, we examined the effects of CPP (3-(2-carboxypiperazin4-yl)propyl-L-phosphonic acid), a competitive NMDA receptor antagonist, on predator stress-induced changes in pCREB-lir in brain areas implicated in fearful and anxious behavior. Areas examined included the amygdala, periqueductal gray (PAG), bed nucleus of the stria terminalis (BNST), anterior cingulate cortex (ACC), and dorsal medial hypothalamus (DMH). CPP blocked the predator stress-induced increase in pCREB-lir in the right lateral PAG and in several amygdala nuclei. CPP also reversed the predator stress-induced suppression of pCREB-lir in the BNST. Importantly, at least in the amygdala and PAG, the pattern of pCREB-lir was hemisphere- and AP plane-dependent. Our results suggest that several amygdala nuclei, the PAG, and the BNST, where predator stress changes pCREB-lir in a NMDA receptor-dependent manner, are candidate areas of neuroplastic change contributing to lasting changes in anxiety-like behaviors.

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Abbreviations:
ACC, anterior cingulate cortex
ACo, anterior cortical amygdala
AP, anterior–posterior
ALB, anxiety-like behavior
BAOT, bed nucleus of the accessory olfactory tract
BNST, bed nucleus of the stria terminalis
BLa, basolateral amygdala
BLv, ventral basolateral amygdala
BM, basomedial amygdala
Ce, central amygdala
dPAG, dorsal PAG
EPM, elevated plus maze
E, exposed to a cat
ECPP, CPP plus cat exposure
EC, cat exposed combined group—E+VE
ICC, immunocytochemistry
PAG, periaqueductal gray
La, lateral amygdala
Me, medial amygdala
pCREB, phosphorylated cyclic AMP response element binding protein
PCo, posterior cortical amygdala
PKA, protein kinase A
PTSD, posttraumatic stress disorder
lPAG, lateral column of the PAG
NGS, normal goat serum
OD, optical densitometry
PAG, periaqueductal gray
PBS, phosphate-buffered saline
VAB, ventral angular bundle
VC, vehicle handled control
VE, vehicle plus cat exposed
vPAG, ventral PAG

1. Introduction

There is growing interest in the long-lasting changes in brain and behavior that occur after stressful events, an interest heightened by the fact that fearful events may precipitate affective psychopathologies (Harvey and Rapee, 2002; Yehuda, 2002). In extreme cases, a single aversive experience may induce posttraumatic stress disorder (PTSD) (North et al., 1999; Silver et al., 2002). Animal models are useful in the study of the impact of stress on brain and behavior, because they permit simulation of a human condition in a controlled setting which allows the disorder to be studied as it develops. Conditioned fear paradigms, behavior in unfamiliar situations that are fear or anxiety provoking, and more recently, predator stress, are all models used to understand the neurobiology of fearful events.

Predator stress involves the unprotected exposure of a rat to a cat (Adamec and Shallow, 1993). It has been argued that predator stress models aspects of PTSD for several reasons. First, this model has a high degree of ecological validity due to the natural threat posed by the predatory nature of the stressor. Second, duration of anxiety-like effects in rats after predator stress, as a ratio of life span, is comparable to the DSM IV duration of psychopathology required for a diagnosis of chronic PTSD in humans. Third, this model has neurobiological face validity in that right amygdala and hippocampal circuitry are implicated in behavioral changes produced by predator stress, and these areas are consistent with brain areas thought to be involved in PTSD (Adamec, 1997; Adamec et al., 2005a,b, 2006a). For example, brain imaging studies implicate hyperexcitability of the right amygdala in response to script-driven trauma reminders in the etiology of PTSD (Rauch et al., 1997; Rauch and Shin, 1997; Shin et al., 1997, 2004) (Shin et al., 1999). Fourth, parallel path analytic studies have been done using data from Vietnam veterans suffering from PTSD and predator stressed rodents to determine if analogous relationships exist between instigating conditions and subsequent changes in affect. In both humans and rodents, features of the stressor predict the level of anxiety (Adamec, 1997). In the predator stress model, for example, the more cat bites received, the higher the level of anxiety measured a week later in the rat. Finally, similar lasting changes in startle and