ELSEVIER

Pharmacology, Biochemistry and Behavior 71 (2002) 379–392

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction

David L. Walker, Michael Davis*

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Woodruff Memorial Building, 1639 Pierce Drive, Suite 4000, Atlanta, GA 30322, USA

Received 14 June 2001; received in revised form 24 September 2001; accepted 25 September 2001

Abstract

Using a paradigm known as fear-potentiated startle, we have examined the neurobiological substrates of Pavlovian fear conditioning. In these experiments, rats are trained to fear an initially neutral stimulus by pairing that stimulus with shock. The amount of fear elicited by the stimulus [i.e., now a conditioned stimulus (CS)] is later assessed by presenting startle-eliciting noise bursts both in the presence and also the absence of the CS. After training, startle responses are typically greater in the presence of the CS. Findings reviewed here suggest that amygdala *N*-methyl-D-aspartate (NMDA) receptors play a key role in triggering the neural changes that support fear learning and also the loss of fear that accompanies extinction training. Amygdala (±)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors also participate in fear learning. However, unlike NMDA receptor antagonists, AMPA receptor antagonists also block fear-potentiated startle when infused prior to testing. Very recent data indicate that glutamate metabotropic Group II receptor agonists also block fear learning when infused into the amygdala prior to training, and block fear-potentiated startle when infused prior to testing. A fuller understanding of the role of amygdala glutamate systems in fear and fear learning may suggest novel pharmacological approaches to the treatment of clinical anxiety disorders.

Keywords: Glutamate; Metabotropic receptor; *N*-methyl-D-aspartate; Fear learning; Fear-potentiated startle; Anxiety; Amygdala; D-Cycloserine

1. Introduction

The amygdala is a group of spatially contiguous and anatomically interconnected nuclei located within the rostral pole of the temporal lobe of mammals. A prominent role for the amygdala in the evaluation of biologically significant stimuli and in the generation of responses to such stimuli has long been recognized, and has been particularly well documented with respect to fear-evoking stimuli (e.g., Blanchard and Blanchard, 1972; Goddard, 1964; Robinson, 1963; Slotnick, 1973). In recent years, it also has become evident that the amygdala plays an important role in fear learning (e.g., Davis, 2000; Fendt and Fanselow, 1999)

For several years now, we have examined the role of the amygdala in fear and fear learning using fear-potentiation of the acoustic startle reflex as a behavioral measure. For these experiments, rats are trained by pairing a brief initially neutral stimulus (most often a 3.7-s light, although tones and olfactory stimuli have also been used) with a 0.5-s footshock unconditioned stimulus (US). Rats are later tested by presenting them with a series of startle-eliciting noise bursts. Some of these noise bursts are presented in the presence of the stimulus that had previously been paired with shock, while others are presented in its absence. Fear-potentiated startle is defined as an increase in startle amplitude in the presence versus the absence of the conditioned fear stimulus (Fig. 1). The stimulus does not itself elicit a startle response but, instead, elicits a state of fear that potentiates startle responses to other stimuli.

2. The role of the amygdala and its efferent projections in fear-potentiated startle

The brainstem circuit that mediates the primary acoustic startle response consists of three sets of synapses: those made by spiral ganglion cells within the cochlea onto

* Corresponding author. Tel.: +1-404-727-3591; fax: +1-404-727-3436.

E-mail address: mdavis4@emory.edu (M. Davis).

0091-3057/02/$ – see front matter
PII: S0091-3057(01)00698-0