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The microinjection of a cannabinoid agonist into the accumbens shell induces anxiogenesis in the elevated plus-maze

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ABSTRACT

This study investigated the effect of a cannabinoid agonist injected into the shell region of the nucleus accumbens (nAcbSh) on anxiety-related behaviors. The animals (male Wistar rats) were unilaterally microinjected with either ACEA (arachidonyl-2′-chloroethylamide a CB1 receptor agonist) at doses of 0.005, 0.05 or 0.5 pmol, or vehicle (ethanol 0.04% in saline 0.9%) and submitted to the elevated plus-maze (EPM), a pre-clinical test of anxiety. The data showed that rats microinjected with ACEA (0.05 pmol/0.2 μl) into the AcbSh exhibited decreased % open arm time and open arm entries in comparison with the control group, which is compatible with an anxiogenic-like effect. To rule out the hypothesis that spread of the drug into the ventricle, was responsible for the observed anxiogenic effect, 0.05 pmol ACEA was injected into the lateral ventricle and shown not to alter the responses representative of fear/anxiety and locomotion. The locomotor activity was not changed at the dose of 0.05 pmol ACEA microinjected into the nAcbSh. The present data suggest that activation of cannabinoid receptors in the nAcbSh may modulate fear/anxiety in the EPM.

1. Introduction

Cannabinoid receptors belong to the family of G protein-coupled receptors. Endocannabinoids are synthesized in neuronal cells and then taken up and inactivated by hydrolyzation by neuronal and glial cells. (Di Marzo et al., 1998). Endogenous endocannabinoids (ECBs) represent a class of lipid molecules that play an important role in stress (Riebe and Wotjak, 2011), emotionality (McLaughlin and Gobbi, 2012), post-traumatic stress disorder (Akirav, 2013a; Hauer et al., in press; Neumeister, 2013; Trezza and Campolongo, 2013), emotional memory and learning (Akirav, 2013b; Anastasio, 2013; Giné et al., 2013). The endocannabinoid system modulates diverse neurotransmitter systems and is responsible for many states, including emotional, motivational, cognitive and aging. (Clapper et al., 2009; Mechoulam and Parker, 2013; Bilkei-Gorzo, 2012).

The literature demonstrates an important role for the endocannabinoid system, especially CB1 receptors in mood disorders (Witkin et al., 2005). Pharmacological manipulations that increase the activity of ECBs modulate anxiety-like behavior in animal models of anxiety such as the elevated plus maze (EPM) (Sink et al., 2010; Bortolato et al., 2006; Patel and Hillard, 2006; Braida et al., 2007; Ribeiro et al., 2009) and the light/dark box test (Rutkowska et al., 2006; Scherma et al., 2008).

Microinjection studies with drugs that alter the activity of ECBs reveal that the amygdala, hippocampus (dorsal and ventral) and the dorsolateral periaqueductal gray (dlPAG) are sites where ECBs can modulate anxiety levels (Campos et al., 2010; Roohbakhsh et al., 2007, 2009; Lisboa et al., 2008; Moreira et al., 2007; Zarrindast et al., 2008). In addition, CB1 receptors have been identified across the limbic system, as well as co-expression of CB1 and dopamine and serotonin receptors in rat's forebrain (Hermann et al., 2002). The presence of CB1 receptors has also been shown in the nucleus accumbens (nAcb) (Tsou et al., 1998).

The nAcb is an important area of the basal forebrain, involved in many behaviors, such as motor activity (Gargiulo, 1996), motivation and reward (Koob, 2005, 2013; Salamone, 1994), cognition (Annet et al., 1989; Seamans and Phillips, 1994; Setlow and McGaugh, 1998; Usiello et al., 1998), sexual behavior (Damsma et al., 1992), stress (Abercrombie et al., 1989), and ingestive and defensive behaviors (Lopes et al., 2007). The nAcb is a heterogeneous structure anatomically divided into a core area (responsible for motor functions) and a shell (mainly responsible for limbic functions) (Zahm and Brog, 1992).

The nAcb shell region receives influence from a wide variety of neurochemical systems (Heimer et al., 1991; Zahm and Brog, 1992), such as glutamate, opioid peptides, dopamine, norepinephrine and GABA. This influence may be modulating, through the nAcb shell, different aspects of fear conditioning (Pezze and Feldon, 2004), anxiety (Kochenborger et al., 2012; Lopes et al., 2007; Reynolds and Berridge, 2003; Da Cunha

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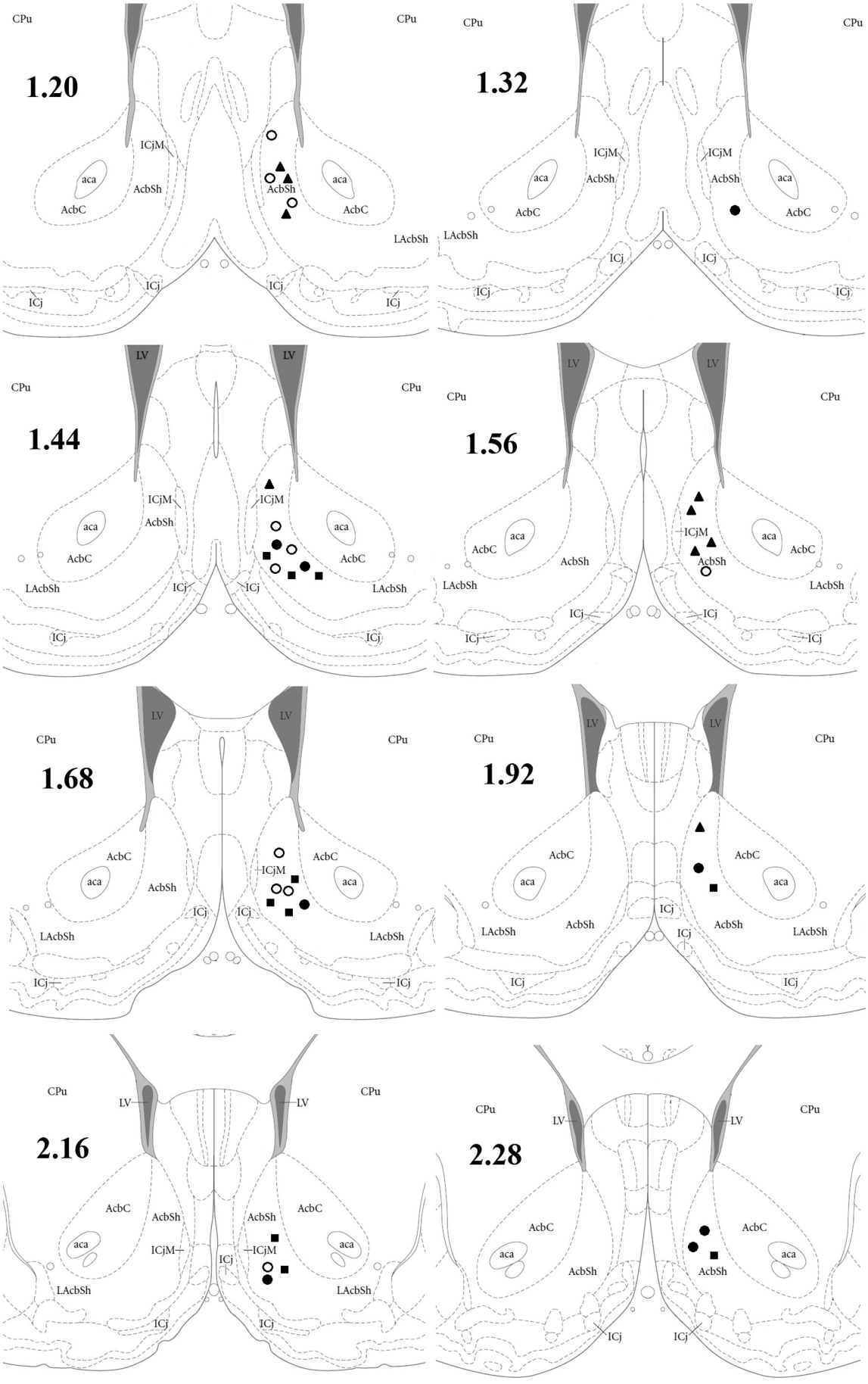

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