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SCIENCE DIRECT
Life Sciences 79 (2006) 30–37
Life Sciences
www.elsevier.com/locate/lifescie

Diurnal variation of arachidonoylethanolamine, palmitoylethanolamide and oleoylethanolamide in the brain of the rat

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Received 22 August 2005; accepted 14 December 2005

Abstract

The diurnal variations of the endocannabinoid arachidonoylethanolamine (anandamide, ANA) as well as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) were detected and quantified in cerebrospinal fluid (CSF), pons, hippocampus, and hypothalamus in the rat over 24 h using HPLC/MS.

In CSF, the 3 compounds presented an increase in their concentration during the lights-on period and a remarkable decrease in their values during the lights-off period. In the pons, ANA, PEA and OEA showed the maximum values during the dark phase. On the other hand, we found that in the hippocampus, ANA increased its concentration during the lights-off period and PEA showed the highest peak at the beginning of the same period. OEA concentration showed no diurnal variations in the hippocampus. Finally, in the hypothalamus, ANA rose during the lights-on period whereas PEA and OEA presented the highest concentration at the end of the lights-off period.

We postulate that all compounds are likely to be accumulated in parenchyma during the lights-off period (when animal is awake) and then, released into the CSF in order to reach target regions in turn to modulate diverse behaviors, such as feeding and sleep.

Keywords: Sleep; Pons; Memory; Rhythms; Hippocampus

Introduction

The amides of long-chain fatty acids with ethanolamine comprise a family of lipid-signaling molecules (Lambert and Di Marzo, 1999) that includes palmitoylethanolamide (Calignano et al., 2001), oleylethanolamide (OEA; Rodriguez de Fonseca et al., 2001) and arachidonoylethanolamine (anandamide, ANA), the first endogenous agonist for cannabinoid receptors identified (Devane et al., 1992).

The presence and distribution of ANA in the central nervous system (CNS) has been demonstrated with localization in hippocampus and brainstem (Felder et al., 1996; Bisogno et al., 1999). PEA and OEA have also been detected in biological samples (Giuffrida and Piomelli, 1998; Giuffrida et al., 2000).

Pharmacologically ANA mimics many of the effects caused by Δ^9- tetrahydrocannabinol (THC), the primary psychoactive molecule in marijuana (Gaoni and Mechoulam, 1964), on diverse behaviors such as memory disruption, hypolocomotion hyperphagia, and sleep (Fride and Mechoulam, 1993; Smith et al., 1994; Wiley et al., 1995; Murillo-Rodríguez et al., 1998; Williams and Kirkham, 1999; Murillo-Rodríguez et al., 2001, 2003).

Recent studies report that PEA displays some biological properties. For instance, Calignano and co-workers (2001) reported that this compound acted as antinociceptive molecule. Capasso et al. (2001) showed that PEA significantly decreased intestinal transit whereas its anti-inflammatory properties have been described (Costa et al., 2002; Lambert et al., 2002; Lo Verme et al., 2005).

Finally, OEA has little or no effect on formalin-evoked pain behavior (Calignano et al., 2001) and it might be involved in satiety mechanisms (Inui, 2004). Its anorexic action in rats is not blocked by cannabinoid receptors-specific antagonists (Rodriguez de Fonseca et al., 2001). Our group has described that peripheral administrations of OEA delayed feeding onset in a dose-dependent manner (Gaetani et al., 2003). Importantly, the

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0024-3205/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.lfs.2005.12.028

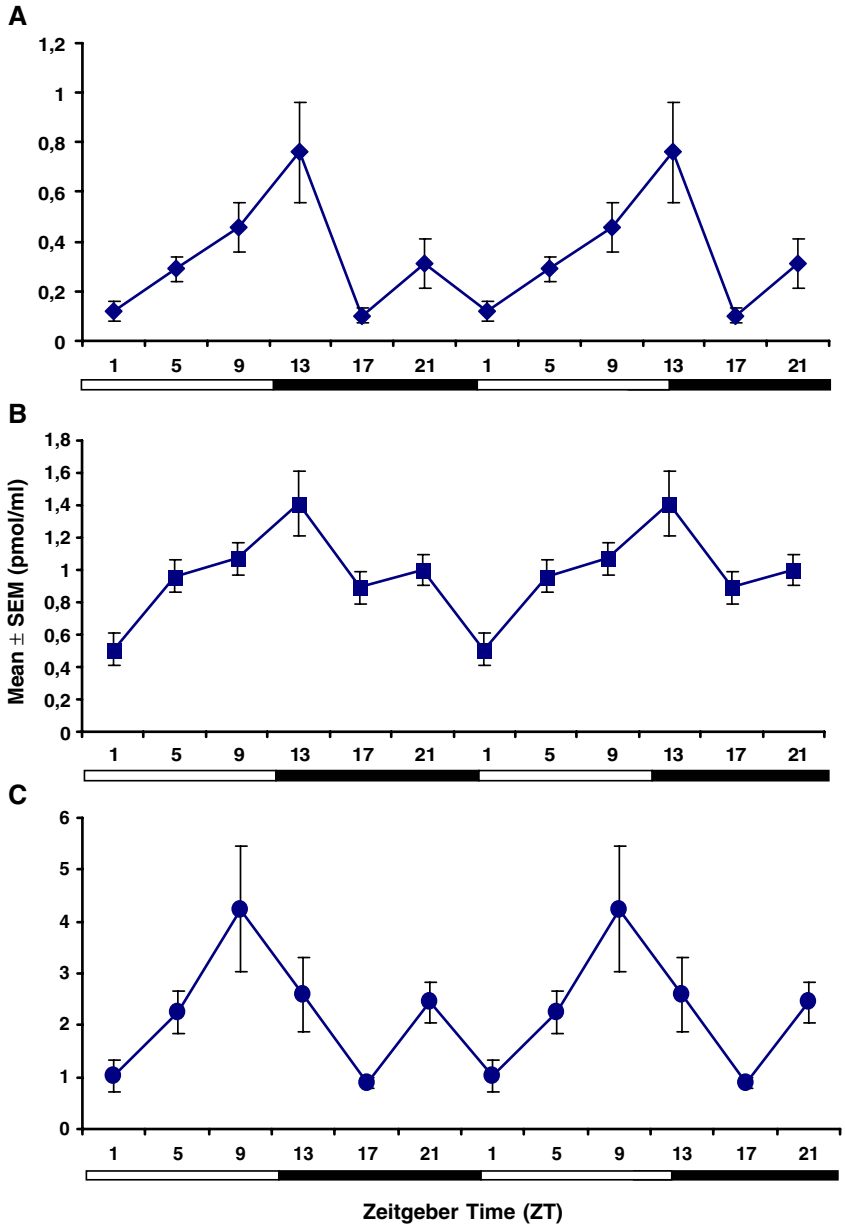

Fig. 1. Daily rhythm in (A) ANA, (B) PEA and (C) OEA in CSF collected from animals during a light–dark phase (open horizontal bars represent the light period; the dark period is indicated by the closed horizontal bars). Double plotted values are expressed as the mean ± SEM ($n=5$ per time point; $F=3.6408$, ANOVA, $p<0.008$; PEA ZT1 vs. PEA ZT13 $p<0.01$ by Bonferroni. $F=3.0475$, ANOVA, $p<0.02$; OEA ZT1 vs. OEA ZT9 $p<0.05$ by Bonferroni; OEA ZT9 vs. OEA ZT 17 $p<0.05$ by Bonferroni).

anorexic effect involves a PPAR-alpha, a nuclear receptor that regulates lipid metabolism (Fu et al., 2003). Among the biological effects caused by OEA, it has been reported that this lipid activates the capsaicin receptor channel TRPV1 (Ahern, 2003). This result suggests that TRPV1 could be an alternative biological target for this lipid.

Since amides of long-chain fatty acids with ethanolamine are present in biological fluids (Giuffrida and Piomelli, 1998; Schuel et al., 2002) as well as in CNS (Felder et al., 1996; Bisogno et al., 1999), we investigated the fluctuations of those compounds over 24 h. Specifically, the present study analyzed the circadian variations of ANA, PEA and OEA in cerebrospinal fluid (CSF) as well as in the pons, the hippocampus, and the hypothalamus.

Material and methods

Chemicals

Deuterated standards ([$^2H_4$]ANA), [$^2H_4$]PEA and [$^2H_4$]OEA were synthesized in our lab as described before (Giuffrida and Piomelli, 1998). All other chemicals used were obtained from Sigma Chemicals (St. Louis, MO, USA).

Animals

Adult male Sprague–Dawley rats (215–230 g; Charles River, USA) were housed at constant temperature (21 ± 1 °C) under controlled light–dark cycle (lights on: 07:00–19:00 hours).