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COLOCALIZATION PATTERN OF CALBINDIN AND COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT IN THE MAMMILLARY BODY–ANTERIOR THALAMIC NUCLEI AXIS OF THE GUINEA PIG

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Abstract—The study describes for the first time the colocalization pattern of calbindin (CB) and cocaine- and amphetamine-regulated transcript (CART) in the mammillary body (MB) and anterior thalamic nuclei (ATN) – structures connected in a topographically organized manner by the mammillothalamic tract (mtt). Immunohistochemical study was performed on fetal (E40, E50, E60), newborn (P0) and postnatal (P20, P80) brains of the guinea pig, but the coexistence pattern of the substances was invariable throughout the examined developmental stages. CB and CART colocalized in the perikarya of the lateral part of the medial mammillary nucleus (MMl), whereas in its medial part (MMm) only CB was detected. In the mtt, which originates from the MB, both the substances were present and colocalized in single fibers. Next, fibers from the mtt spread toward the ATN in a particular way: fibers containing CB ran to both the anteromedial thalamic nucleus (AM) and anteroventral thalamic nucleus (AV), while fibers containing CART ran mostly to the latter one. In the ventral part of AV, CB and CART colocalized vastly in the neuropil. The lateral mammillary nucleus and anterodorsal thalamic nucleus were virtually devoid of CB- and CART-positive structures. Based on the known connections between the MB and ATN, we conclude that the studied substances may cooperate in the MMl–AV part of the axis and CB plays a significant role in the MMm–AM part. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: calbindin, cocaine- and amphetamine-regulated transcript, anterior thalamic nuclei, mammillary body, guinea pig, brain development.

INTRODUCTION

The mammillary body–anterior thalamic nuclei axis (MB–ATN axis) is an important component of the so-called extended hippocampal memory system, which also includes the hippocampus, fornix, cingulum bundle and cingulate cortex. All these structures are interconnected in a special way, i.e. hippocampal formation (via fornix)–MB (via mammillothalamic tract)–ATN (via internal capsule)–cingulate gyrus (via cingulum and perforant path)–hippocampal formation (Aggleton and Brown, 1999). To date, numerous clinical and behavioral studies have shown that functions of the system are closely related to some mnemonic processes such as spatial and episodic memory. For example, pathology in structures of the MB–ATN axis in humans leads to diencephalic amnesia (Ghika-Schmid and Bogousslavsky, 2000; Harding et al., 2000; Van der Werf et al., 2003; Gold and Squire, 2006), whereas lesions of these structures in animals disrupt spatial learning tests (Aggleton et al., 1995; Byatt and Dalrymple-Alford, 1996; Sziklas and Petrides, 1999; Van Groen et al., 2002; Vann and Aggleton, 2003; Moreau et al., 2013). Moreover, it has been shown that the MB–ATN axis may also be involved in the modulation of emotional and motivational states (Papez, 1995; Ghika-Schmid and Bogousslavsky, 2000; Young et al., 2000; Xiao and Barbas, 2002a,b; Bernstein et al., 2007). Results of several studies have suggested that each nucleus within the axis, in regard to its connections and electrophysiological properties, may play a different role in the processes mentioned (Vertes et al., 2001; Xiao and Barbas, 2002a; Albo et al., 2003; Vann et al., 2007; Aggleton et al., 2010). The MB reaches the ATN via mammillothalamic tract (mtt) and these projections are topographically organized (Watanabe and Kawana, 1980; Shibata, 1992; Aggleton et al., 2010). Significantly, almost every neuron within the MB projects to the ATN (Vann et al., 2007; Aggleton et al., 2010).

Recently, Abrahám et al. (2007) have reported that calbindin (CB) D_{28k} together with cocaine- and amphetamine-regulated transcript (CART) peptide may be involved in the development of the hippocampus in the rat. It was proposed that both CB and CART peptide play neuromodulatory role in nervous cells of the dentate gyrus, while CART peptide may additionally exert neurotrophic functions in some developmental events, and these may be related to synaptogenesis and spine formation.

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Abbreviations: AD, anterodorsal nucleus; AM, anteromedial nucleus; ATN, anterior thalamic nuclei; AV, anteroventral nucleus; AVv, ventral part of the anteroventral nucleus; CART, cocaine- and amphetamine-regulated transcript; CB, calbindin; ir, immunoreactive; MB, mammillary body; ML, lateral mammillary nucleus; MM, medial mammillary nucleus; MMl, lateral part of medial mammillary nucleus; MMm, medial part of medial mammillary nucleus; mtt, mammillothalamic tract.

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Our previous immunohistochemical study has shown that CB appears in perikarya of the guinea-pig ATN not before 20th postnatal day, but is vastly present in fibers and terminal-like boutons since 40th day of the fetal development (Żakowski et al., 2013). Based on several studies on adult rats (Celio, 1990; Séquier et al., 1990; Frassoni et al., 1991; Battaglia et al., 1992; Rogers and Résibois, 1992; Arai et al., 1994), we assumed that these early arrived CB-immunoreactive (CB-ir) structures in the ATN continue with axons in the mtt. Likely, CB exerts some significant functions during development of central nervous system, i.e. neuromodulatory function (Molinari et al., 1996; Jouvenceau et al., 1999; Abrahám et al., 2007), influence on synapse plasticity and synaptically-evoked Ca^{2+} transients in neuron dendrites (Schwaller et al., 2002), involvement in synaptogenesis (Murray et al., 2007) and neuroprotection (D'Orlando et al., 2001, 2002).

Neurotrophic functions of CART peptide, its involvement in neuroprotection and development of central nervous system have been reported several times (Dun et al., 2001; Brischoux et al., 2002; Risold et al., 2006; Bharne et al., 2012). Moreover, studies on rats have shown that CART peptide may be involved in spatial learning and memory related behavior (Upadhya et al., 2011), while Yermolaieva et al. (2001) have shown that CART peptide targets hippocampal voltage-gated Ca^{2+} channels, and they have proposed a role for the peptide in helping to shape the neuronal plasticity associated with learning and memory. CART peptide has been also found in the hippocampus of the guinea pig (Kolenkiewicz et al., 2009).

Taking into account results of the studies concerning possible involvement of CB and CART peptide in both mnemonic processes and development, it seems quite interesting to reveal their colocalization pattern in the developing MB–ATN axis. To date, there is a lack of studies concerning relations of these substances in the axis in both the adult and developing mammalian brain. Therefore, the aim of the study was to describe a distribution pattern of CB and CART peptide in the MB–ATN axis of the guinea pig at several developmental stages since 40th fetal day to 80th postnatal day.

EXPERIMENTAL PROCEDURES

Tissue preparation

All experimental protocols were approved by the Local Ethics Commission for Animal Experimentation at University of Warmia and Mazury in Olsztyn, Poland (in accordance with European Union (EU) Directive 2010/63/EU for animal experiments). The study was performed on brains of the Dunkin-Hartley guinea pigs (*Cavia porcellus*) at several developmental stages: E40, E50, E60 (40th, 50th, 60th day of gestation; $n = 3$ for each stage), P0 (newborn, $n = 3$), P20 and P80 (20th and 80th day after birth; $n = 3$). All procedures of the tissue preparation are described in detail in our previous publication (Żakowski and Robak, 2013).

Immunohistochemical procedures

Sections through the MB and anterior thalamus from the postnatal and fetal brains were processed for two immunohistochemical methods: a routine double-labeling immunofluorescence and a single-labeling DAB method.

For the first method we used solution of rabbit polyclonal antibody raised against CB (1:4000, Swant, CH-6501 Bellinzona, Switzerland) and solution of mouse monoclonal antibodies raised against CART peptide (1:10,000, R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN 55413, USA). In order to show the binding sites of the antibodies, the sections were incubated with mixtures of secondary antibodies: FITC-conjugated-anti-rabbit (1:800, Jackson ImmunoResearch Laboratories, Inc., 872 West Baltimore Pike, West Grove, PA, USA) and Cy3-conjugated-anti-mouse (1:10,000 Jackson ImmunoLabs, USA). For DAB method we used solutions of the same primary antibodies, but in different final concentrations: 1:1000 for anti-CB and anti-CART. Both methods were described in detail by Żakowski and Robak (2013).

To test both antibody and method specificity various controls were applied. To test primary antibodies specificity, antisera produced in different species and/or provided by other manufacturers were tested on the same sections according to the routine double-immunofluorescence. The staining patterns were identical for all variants used. The secondary antisera were tested by the omission and replacement of primary antisera by nonimmune sera or PBS. Moreover, both immunofluorescence and DAB method produced the

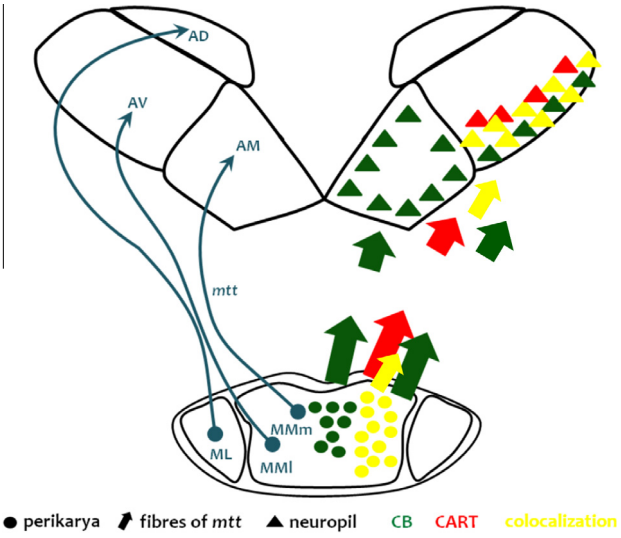

Fig. 1. Schematic drawing showing the mammillary body–anterior thalamic nuclei axis (MB–ATN axis) in the guinea-pig brain. (Left) Connections between the MB and ATN in accordance to Aggleton et al. (2010). (Right) The distribution and colocalization patterns of calbindin and cocaine- and amphetamine-regulated transcript peptide. *Abbreviations:* AD, anterodorsal nucleus; AM, anteromedial nucleus; AV, anteroventral nucleus; CART, cocaine- and amphetamine-regulated transcript; CB, calbindin; ML, lateral mammillary nucleus; MMl, lateral part of medial mammillary nucleus; MMm, medial part of medial mammillary nucleus; mtt, mammillothalamic tract.

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