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KOMUNIKAT O WYNIKACH BADAŃ
BRIEF REPORT

Orexin receptor-1 expression in edult rodent neurogenic regions: evidence from the subgranular zone and the median eminence

Ekspresja receptora oreksynowego-1 w regionach neurogenezy dorosłych gryzoni: strefie podziarnistej oraz wyniosłości pośrodkowej

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ABSTRACT

INTRODUCTION: Orexin signaling plays a vital role in regulating autonomic and cognitive functions, including sleep-wake cycles, feeding, and memory. Orexin receptor-1 (OX_1R), a key component of this system, may also influence adult neurogenesis. This study examined OX_1R expression in both the classic (hippocampal) and non-classic (hypothalamic) neurogenic regions of the adult rodent brain.
MATERIAL AND METHODS: Adult rodent brains were fixed, paraffin-embedded, and sectioned coronally. Immunohistochemistry and immunofluorescence were performed using antibodies against OX_1R, DCX, and TUC-4, followed by fluorophore- or diaminobenzidine-based detection. Negative controls were included to ensure specificity.
RESULTS: OX_1R-positive cells were localized primarily to the subgranular zone (SGZ) of the dentate gyrus and β2 tanycytes of the median eminence showed uniform OX_1R expression in both somata and vascular-directed processes. Morphological variation was observed between species, with diverse perikaryon shapes in mice and predominantly elongated, multipolar forms in rats.
CONCLUSIONS: This study revealed, for the first time, region-specific OX_1R expression in the SGZ in β2 tanycytes of the median eminence. These findings suggest a potential role for orexin signaling in adult neurogenesis.

KEYWORDS

orexin, adult neurogenesis, hippocampus, tanycytes

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STRESZCZENIE

WSTĘP: Sygnalizacja oreksynergiczna odgrywa kluczową rolę w regulacji funkcji autonomicznych i poznawczych, w tym cyklu snu i czuwania oraz przyjmowania pokarmu. Receptor oreksyny-1 (*orexin receptor-1* – OX_1R), pierwszoplanowy element tego układu, może również wpływać na neurogenezę w mózgu dojrzałym. W przedstawionym badaniu zbadano ekspresję OX_1R zarówno w klasycznych (hipokamp), jak i nieklasycznych (podwzgórze) regionach neurogennych mózgu dorosłych gryzoni (szczurów i myszy).

MATERIAŁ I METODY: Mózgi dorosłych gryzoni utrwalono, zatopiono w parafinie i skrojono w płaszczyźnie poprzecznej. Badania immunohistochemiczne i fluorescencyjne wykonano z wykorzystaniem pierwszorzędowych przeciwciał selektywnych względem OX_1R, DCX i TUC-4, a następnie przeciwciał drugorzędowych sprzężonych z fluorochromami lub w reakcji diaminobenzydyny. W celu zapewnienia swoistości uwzględniono kontrole negatywne.

WYNIKI: Komórki OX_1R-pozytywne zlokalizowano głównie w strefie podziarnistej (*subgranular zone* – SGZ) zakrętu zębatego, β2-tanycyty wyniosłości pośrodkowej wykazywały jednorodną ekspresję OX_1R zarówno w ich ciałach komórkowych, jak i w wypustkach okołonaczyniowych. Zaobserwowano istotne zróżnicowanie morfologiczne neuronów OX_1R-pozytywnych między badanymi gatunkami gryzoni – u myszy dominowały perykariony różnokształtne, natomiast u szczurów komórki wydłużone i wielobiegunowe.

WNIOSKI: Badanie to po raz pierwszy ujawniło specyficzną dla regionu ekspresję OX_1R w SGZ hipokampa oraz w β2-tanycytach wyniosłości pośrodkowej podwzgórza. Wyniki sugerują potencjalną rolę sygnalizacji oreksynowej w regulacji neurogenezy w mózgu dojrzałym.

SŁOWA KLUCZOWE

oreksyna, neurogeneza w mózgu dojrzałym, hipokamp, tanycyty

INTRODUCTION

Neurochemical research on brain neuropeptides involved in the regulation of adult neurogenesis has emerged as a highly dynamic area in contemporary neuroscience. Two well-established neurogenic niches have been identified in the vertebrate brain: the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) beneath the ependyma of the lateral ventricles. The SGZ gives rise to granule neurons within the hippocampus, while the SVZ produces progenitor cells that migrate via the rostral migratory stream to the olfactory bulb, where they differentiate into specialized sensory interneurons. The SGZ niche is primarily composed of astrocytes and capillary endothelial cells, both of which are abundantly represented in this layer of the dentate gyrus [1,2]. In addition to these canonical regions, two potential sites of adult neurogenesis have recently been found within the hypothalamus: the hypothalamic ventricular zone (HVZ), situated along the lateral walls of the third ventricle, and the hypothalamic proliferative zone (HPZ), composed primarily of median eminence tanycytes [3,4] whose somata are situated along the floor of the third ventricle. Based on their anatomical distribution and the expression of specific markers related to lineage and differentiation, radial glia-like tanycytes are classified into four subtypes: α1, α2, β1, and β2 [5]. α1 tanycytes are found at the ventromedial and dorsomedial nuclei of the hypothalamus, α2 tanycytes are in the vicinity of the arcuate nuclei, and the β1 and β2 types are situated along the HVZ (ventral tanycytic zone) of the third ventricle [6], but extend their processes into the median eminence, in the tuberal region of the hypothalamus [7]. Notably, β2 tanycytes are characterized by their remarkable sensitivity to circulating hormones, metabolic regulators, and nutritional signals. Their somata, embedded in the ependymal lining, are optimally placed to detect molecular cues from the cerebrospinal fluid (CSF), while their elongated processes extend toward the median eminence, where they may interact with blood-borne signals [8]. Given their strategic location at the interface between the CSF and hypothalamic vasculature, β2 tanycytes could be well positioned to respond to neuropeptides such as orexins. Tanycytes comprising the HVZ – including β2 tanycytes in both rats and humans – express several neural precursor markers, including nestin [9], Sox2 [10], vimentin [11], and doublecortin-like protein [12], suggesting a role in adult neurogenesis.

In parallel, orexins exert broad regulatory effects across the central nervous system, influencing diverse physiological domains from sleep and homeostasis to memory, emotions, and reward [13,14]. Orexinergic perikarya, which co-express glutamate and dynorphine, are localized exclusively in the perifornical area and the lateral and posterior hypothalamus [15,16,17]. Their axons target multiple brain regions, including key neurogenic areas such as the hippocampus and the olfactory bulb [18,19]. Orexins act via two G-coupled receptors, known as OX_1R (orexin receptor-1) and OX_2R, showing significant homology among mammalian species [20]. OXRs have been identified in various brain regions, including the prefrontal and limbic cortices, the hippocampus, the amygdala, the bed nucleus of stria terminalis, and several hypothalamic and brainstem nuclei [21,22].

Building on recent evidence which suggests that certain hypothalamic orexin neurons project to neurogenic regions in the rat brain [23], we hypothesized that cells

within both the SGZ and the hypothalamic subependymal zone – particularly β2 tanycytes – may be responsive to orexins via OX_1R signaling. This hypothesis is supported by the anatomical and functional profile of β2 tanycytes: they are strategically positioned to sense hormonal and nutritional cues from both the CSF and the blood and they express multiple markers of neural precursors. These characteristics make them compelling candidates for mediating the neurogenic effects of orexins in the hypothalamus.

Thus, if β2 tanycytes express OX_1R, they could serve as intermediaries through which orexins regulate adult neurogenesis, energy homeostasis, or hormonal feedback in hypothalamic circuits. To explore this possibility, we investigated OX_1R expression within both classic (hippocampal SGZ) and non-classic (hypothalamic median eminence) neurogenic zones.

MATERIAL AND METHODS

Animals

Male Sprague–Dawley rats and mice (N = 5 each) from the Medical University of Silesia Experimental Centre were housed at a temperature of 22°C with a regular 12/12 light/darkness cycle and access to standard Murigran chow and water *ad libitum*. The research was approved by the Local Ethical Commission for Animal Experimentation at the Medical University of Silesia (No. 36/2012) and all experimental procedures were conducted according to the NIH Guide for Care and Use of Animals.

Immunohistochemistry

The animals were quickly anesthetized with isoflurane inhalation and sacrificed. The brains were excised, fixed by immersion for 48 h in 4% paraformaldehyde PBS (pH 7,2–7,4) at 4°C, dehydrated via graded alcohols at room temperature, cleared in xylene, embedded in paraffin, and finally sectioned on a microtome (Leica Microsystems, Germany) in the coronal plane (-2.00 to -2.80 mm from the bregma) into 7-μm thick slices, according to standard rat brain atlases.

For immunofluorescence, after blocking with 0.1% Triton X-100 (Sigma, T-7878) and 10% serum (horse normal serum for orexin, Vector Labs), sections were incubated overnight at 4°C with rabbit antibody against rat orexin-1 receptor (1:2000, Abcam). Additional antibodies against adult neurogenesis markers were applied: goat anti-rat DCX (Santa Cruz Pharmaceuticals, 1:1000) and rabbit anti-rat TUC-4 (Abcam, 1:1000). Primary antibodies were followed by fluorochrome-conjugated secondary antibodies: goat anti-rabbit FITC (1:200, Abcam) for 1 h at 4°C. Finally, the sections were mounted on glass slides with DAPI-containing medium and coverslipped.

For diaminobenzidine (DAB) single staining, blocking (0.1% Triton X-100 and 10% serum) and administration of primary antibodies (1:1000) were followed by biotynylated anti-rabbit/anti-goat secondary antibodies for 30 min, and then an avidin-biotin-horseradish peroxidase complex (Vectastain ABC kit, Vector Labs) for another 30 min, before DAB was used to complete the reaction (1–2 min). The brain sections were dehydrated, mounted on glass slides with medium, and coverslipped. Sections incubated with rabbit/mouse IgG instead of primary antibody were used as negative controls in order to check the specificity of primary antibodies. All images were captured and analyzed with Nikon Coolpix optic systems and processed using Image ProPlus software (Media Cybernetics, USA). The same planes of the brain were chosen from each set of slides. On each section, we analyzed the morphology of immunopositive and immunonegative cells from the entire area of the dentate gyri and lateral hypothalamic regions.

RESULTS

Upon examining the hippocampal area of both mouse and rat brains, a distinct number of granular cells in the dentate gyrus exhibited OX_1R immunoreactivity. The highest aggregation of OX_1R-positive cells was observed almost exclusively within the SGZ, known as the classic site of adult neurogenesis. The OX_1R--immunoreactive cells in the mouse dentate gyri displayed a relatively wide spectrum of shapes: round, oval, fusiform, and even triangular (pyramidal) perikaryal, from which short dendrites sometimes emerged (Figure 1[A–F]). In the rat brain, oval, multipolar, and elongated OX_1R-immunoreactive somata were most common (Figure 1[G–H]). In the hypothalamus, the inner median eminence layer showed distinct, regular OX_1R expression. Columnar cell bodies and long processes running toward blood vessels indicated uniform, mild OX_1R immunoreactivity (Figure 2).

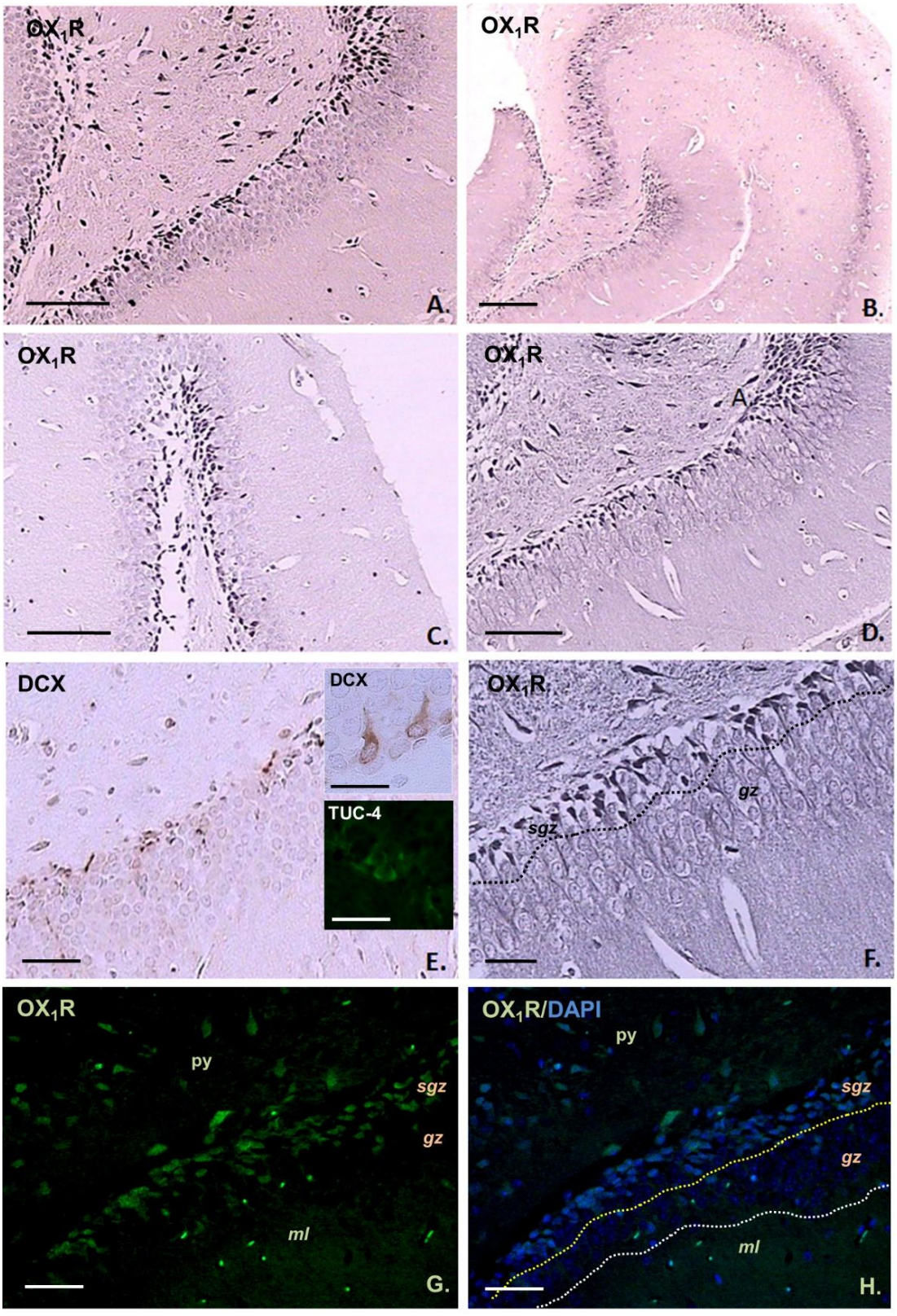

Fig. 1. Orexin receptor-1 (OX_1R)-expressing neurons in the hippocampus. Overview of neuroanatomical OX_1R immunodistribution in the mouse and rat Ammon's horn and dentate gyrus. Immunoperoxidase reaction with DAB staining in mouse hippocampus (A–D, F). Scale bars: 100 μm (A–D), 25 μm (F). Expression of adult neurogenesis markers doublecortin (DCX) and TUC-4 in the rat subventricular zone (E). Scale bars: 50 μm (E), 25 μm (insets). Immunofluorescence for OX_1R in the rat dentate gyrus (G–H). Scale bar: 50 μm. gz – granular zone; ml – molecular layer; py – pyramidal layer; sgz – subgranular zone.

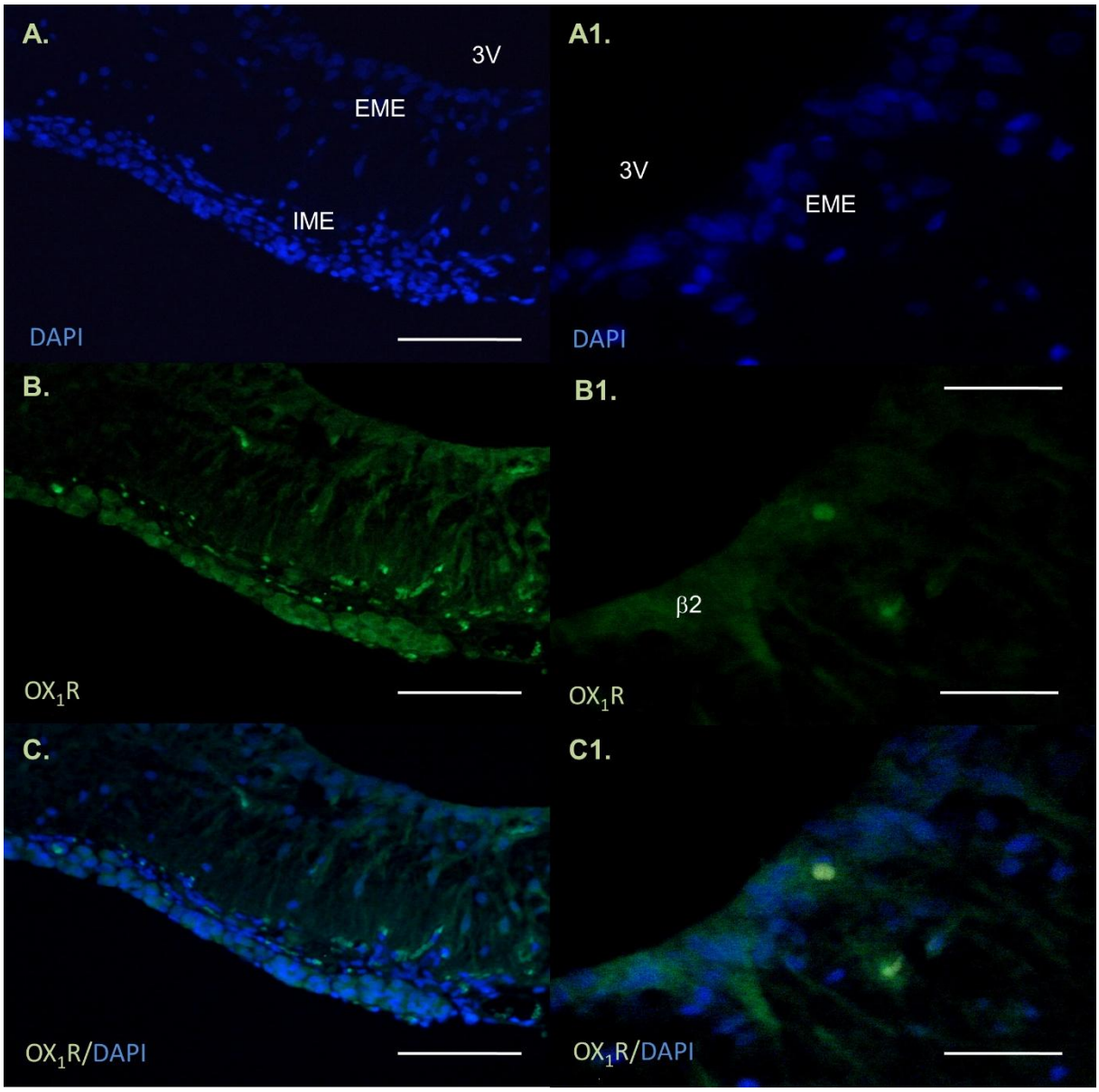

Fig. 2. Orexin receptor-1 (OX_1R)-immunopositive cells in the rat median eminence. Scale bars: 250 μm (A–C), 50 μm (A1–C1). EME – external medial eminence; IME – internal medial eminence; 3V – third ventricle.

DISCUSSION

Our study reveals a region-specific expression of OX_1R, in the SGZ of the dentate gyrus of the hippocampus in both rats and mice. For the first time, it reports strong OX_1R immunoreactivity in the majority of β2 tanycytes within the median eminence of the hypothalamus.

Accumulating evidence suggests that the multidirectional nature of orexin signaling in the brain contributes to a wide range of autonomic and affective processes, including food intake, sleep-wake regulation, stress responses, reward and addiction mechanisms, and the pathogenesis of various neuropsychiatric disorders [24,25,26,27,28,29]. The hippocampus is a well-established target of the orexinergic system, receiving dense projections from the lateral hypothalamus. Orexin receptors – OX_1R and OX_2R – are expressed in complementary patterns across the hippocampal subregions: OX_1R is found in CA1, CA2, and the dentate gyrus, while OX_2R is in the dentate gyrus and CA3 [21,22,30]. These receptors are implicated in diverse hippocampal functions, including reward processing, learning, memory [27,31,32,33], spatial cognition [34], stress response [35,36], and, notably, antinociception [37,38].

Orexin-A in particular has been shown to enhance hippocampal neurogenesis, potentially contributing to cognitive performance. However, whether adult neurogenesis influences the population of orexin--producing neurons remains uncertain [39,40]. For instance, local perfusion of orexin-A into the dentate gyrus promotes structural and functional plasticity [41], while transgenic mice lacking orexin neurons exhibit reduced hippocampal plasticity [42]. Intracerebroventricular orexin-A administration increases cellular proliferation in the dentate gyrus and alleviates depression-like symptoms [43,44].

Similarly, in penthylenetetrazol (PTZ)-kindled rat models of epilepsy, orexin-A boosts proliferation and promotes differentiation of neural precursors in the dentate gyrus [45]. The PTZ-induced kindling model is currently widely used in epileptogenic drug testing. As PTZ induces seizures via glutamatergic excitation and GABAergic inhibition [46], these findings suggest that orexin-A may counteract seizure-induced cognitive deficits through OX_1R-mediated neurogenesis. Reduced orexin-A levels following seizures may partly underlie such impairments [45].

Orexins also stimulate neurogenesis in the SVZ, although its functional relevance remains unclear [23]. It is still debated whether orexin signaling is essential for hippocampal neurogenesis and whether orexinergic neurons themselves can be replenished via adult neurogenesis [39,40].

Some evidence suggests that a limited population of newly generated hypothalamic neurons may express orexin [47]. In this brain region, adult neurogenesis is believed to support adaptive responses to dietary changes [48,49]. Tanycytes play a critical role, as they can sense hormonal and nutritional cues and can differentiate into orexigenic or anorexigenic neurons. However, the identity of tanycyte subtypes serving as true neural stem cells remains controversial. Notably, in seasonally breeding species, hypothalamic neurogenesis is modulated by day length, with increased levels being observed in the short photoperiod in sheep [50]. Similar changes in cell proliferation and tanycyte function align with feeding behavior and seasonal cues in hamsters [51,52].

Our study found that β2 tanycytes in the inner layer of the median eminence displayed consistent OX_1R immunoreactivity in both their columnar somata and vascular-directed processes. Importantly, β2 tanycytes are the most mitotically active tanycyte subtype [53]; they are especially neurogenic in younger animals [54]. These cells express high levels of Hes1 and Hes2 – markers of neural progenitors – and all newly generated neurons remain within the median eminence [54,55]. This local neurogenesis may support a stable population of sensory neurons responsible for monitoring CSF composition.

In addition, OX_1R-immunoreactive cells in dentate gyri displayed a variety of shapes. This intriguing diverse shape pattern is challenging to interpret and may reflect as yet unidentified interspecies differences in cellular morphology. Additionally, we cannot rule out the possibility that certain cells exhibit an irregular immunostaining pattern, potentially confined to the perikarya, thereby rendering some cellular processes undetectable.

It is important to acknowledge the limitations of our preliminary, predominantly qualitative morphological analysis. Future studies should aim to expand upon these findings by incorporating co-expression analyses of OX_1R with established markers of adult neurogenesis. While adult neurogenesis remains a prominent and debated topic in contemporary neuroscience, robust evidence supporting sustained, long-term neurogenesis in the adult human brain remains limited. Moreover, clinical approaches such as stem cell transplantation for neurodegenerative conditions, including Alzheimer's and Parkinson's diseases or ischemic brain injuries, have thus far yielded disappointing therapeutic outcomes [56]. In contrast, numerous animal studies continue to provide valuable insights into the mechanisms of adult neurogenesis, advancing our understanding of brain structure and function.

CONCLUSIONS

Our findings revealed a distinct expression pattern of OX_1R in the dentate gyrus of both rats and mice, specifically confined to the subgranular zone. Moreover, we demonstrated for the first time that the majority of β2 tanycytes within the median eminence exhibit robust OX_1R immunoreactivity. These observations cautiously point to a previously underexplored link between orexin signaling and adult neurogenesis in both the classic hypothalamic neurogenic regions. Nonetheless, further research is necessary to elucidate the functional significance of these potential regulatory interactions.

Compliance with Ethical Standards

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Conflict of interest

The authors declare no conflict of interest.

Authors' contribution

Study design – A. Pinna, A. Pałasz
Data collection – A. Pinna
Data interpretation – A. Pinna, A. Pałasz
Manuscript preparation – A. Pinna, A. Pałasz
Literature research – A. Pinna

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