

Lateral characteristics of oxytocin distribution in the mouse brain following intranasal peptide administration

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ABSTRACT

BACKGROUND: Intranasal administration of oxytocin is an effective method for delivering the hormone to the central nervous system, bypassing the blood-brain barrier. This approach holds significant promise for psychiatric clinical applications. Previous studies have demonstrated that simultaneous oxytocin administration in both nostrils induces lateralized changes in monoamine metabolism in the mouse brain.

AIM: To investigate the lateral characteristics of oxytocin penetration in the brain following intranasal administration.

MATERIALS AND METHODS: Experiments were conducted on 12 male outbred white mice. The experimental group received intranasal oxytocin (5 IU/1 mL, 10 µL per nostril), while the control group received an equivalent volume of saline. Oxytocin levels were measured 15 minutes post-instillation in the hypothalamus, olfactory bulbs, striatum, and hippocampus on both sides of the brain using an enzyme-linked immunosorbent assay (ELISA).

RESULTS: In the control group, oxytocin distribution was symmetric in the olfactory bulb and striatum. However, in the hippocampus, control mice exhibited asymmetry with a higher oxytocin concentration on the right side (p = 0.0192). In the experimental group, oxytocin levels significantly increased in the left hippocampus (p = 0.0223) and hypothalamus (p = 0.0036), with a trend observed in the left olfactory bulb (p = 0.0572).

CONCLUSION: Intranasal oxytocin administration enhances oxytocin penetration into the left side of the brain, primarily through the left olfactory bulb and hippocampus, ultimately reaching the hypothalamus.

Keywords: oxytocin; intranasal administration; hippocampus; brain asymmetry.

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Латеральные особенности распределения окситоцина в головном мозге мышей при интраназальном введении пептида

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Актуальность. Интраназальный способ введения окситоцина рассматривается как эффективный способ его доставки в центральную нервную систему, позволяющий миновать гематоэнцефалический барьер, что делает его перспективным для применения в психиатрической клинике. Ранее было показано, что одновременное введение окситоцина в обе ноздри вызывает унилатеральные изменения обмена моноаминов в головном мозге мышей.

Цель — изучить латеральные особенности проникновения окситоцина в головной мозг при интраназальном введении. Материалы и методы. Эксперименты проведены на 12 самцах белых беспородных мышей. Животным экспериментальной группы интраназально (5 ME/1 мл, по 10 мкл в каждую ноздрю) вводили окситоцин, а мышам контрольной группы — эквивалентный объем физиологического раствора. Уровень окситоцина через 15 мин после инстилляции определяли в гипоталамусе, а также в обонятельных луковицах, стриатумах и гиппокампах левой и правой стороны мозга, используя метод иммуноферментного анализа.

Результаты. У мышей контрольной группы содержание окситоцина в обонятельной луковице и стриатуме было симметричным. Однако в гиппокампе у контрольных мышей была отмечена асимметрия с преобладанием окситоцина справа (*p* = 0,0192). У животных, которым вводили окситоцин, его уровень значимо возрастал в левом гиппокампе (*p* = 0,0223) и в гипоталамусе (*p* = 0,0036); в левой обонятельной луковице была отмечена соответствующая тенденция (*p* = 0,0572). **Выводы.** Можно предположить, что при интраназальном введении окситоцин активнее проникает в мозг с левой стороны, проходя через левую обонятельную луковицу и левый гиппокамп, а в конечном итоге — в гипоталамус.

Ключевые слова: окситоцин; интраназальное введение; гиппокамп; асимметрия мозга.

Как цитировать

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BACKGROUND

The intranasal administration of pharmacological compounds is considered a potentially effective method for delivering substances to the central nervous system (CNS) while bypassing the blood-brain barrier (BBB) [1]. This route of administration appears to be particularly promising for the use of oxytocin as a therapeutic agent for treating psychiatric disorders in humans [2]. Experimental studies in laboratory mice have confirmed that intranasal oxytocin administration can reduce anxiety-like behavior [3] and intraspecific aggression [4-7]. Following intranasal instillation, oxytocin distribution in the brain is uneven, with higher concentrations in the hippocampus than in the striatum [3]. Studies investigating the pathways of neuropeptide distribution, particularly oxytocin, following intranasal administration indicate that these substances can reach the brain directly via olfactory and trigeminal nerve projections [8, 9]. In rodents, oxytocin accumulates in the amygdala and hippocampus [10], and its concentration increases in other forebrain regions rich in oxytocin receptors [11, 12]. Previously, we demonstrated that in mice, simultaneous oxytocin administration into both nostrils induces unilateral changes in monoamine metabolism in the forebrain, affecting either the left or right hemisphere [4-7]. However, no studies have systematically examined lateral differences in the distribution of intranasally administered oxytocin across the left and right sides of the forebrain.

AIM: To investigate the lateral characteristics of oxytocin penetration in the brain following intranasal administration.

MATERIALS AND METHODS

Experiments were conducted on 12 sexually mature male outbred white mice weighing 20–22 g, obtained from the Rappolovo breeding facility (Leningrad Region, Russia). The study adhered to ethical guidelines for the humane treatment of laboratory animals in accordance with the Rules of Laboratory Practice in the Russian Federation.^{*} Before the experiment, the mice were housed in standard vivarium conditions with ad libitum access to food and water for two weeks.

On the day of the experiment, the animals were randomly assigned to two groups. The experimental group (EG, n = 6) received intranasal oxytocin, 10 µL of an ampoule solution containing 5 IU/mL was instilled into each nostril. The control group (CG, n = 6) received an equivalent volume of saline (Dalchimpharm, Russia). Fifteen minutes after instillation, the animals were decapitated.

Seven brain regions were isolated: the left and right olfactory bulbs, corpora striata, hippocampi, and the hypothalamus, which was extracted as a single fragment. The brain tissue was immediately frozen and stored at -70 °C until analysis. Tissue samples were homogenized using a CryoMill vibrational grinder (Retsch, Germany) at -198 °C with liquid nitrogen. The cryogenically milled samples were suspended in 0.5 mL of phosphate-buffered saline (PBS, pH = 7.4). Oxytocin concentrations in different brain regions were measured using an enzyme-linked immunosorbent assay (ELISA) with a high-sensitivity oxytocin detection kit (Cloud-Clone Corp., USA), strictly following the manufacturer's instructions. After the reaction, optical density was measured at 450 nm.

Total protein content was determined using the Bradford assay [13]. Oxytocin concentrations were expressed in pg/mg of protein.

Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Bonferroni's multiple comparisons test as a post hoc analysis. Additionally, Student's *t*-test was applied to assess paired comparisons (differences between the left and right brain structures) and unpaired comparisons (differences between CG and EG).

RESULTS

ANOVA analysis revealed significant differences in oxytocin levels across the examined brain regions in CG mice (*F*[6; 29] = 5.265, p = 0.0009; Fig. 1*a*). The lowest oxytocin concentration was detected in the hypothalamus (4.22 ± 0.31 pg/mg of protein), while the highest level was observed in the right hippocampus (13.61 ± 0.68 pg/mg of protein). Post hoc analysis indicated that the right hippocampus exhibited significantly higher oxytocin levels than the contralateral (left) hippocampus (p < 0.01), hypothalamus (p < 0.001), and both the left and right corpus striatum (p < 0.05 and p < 0.01, respectively; Fig. 1*a*).

In EG mice, ANOVA also demonstrated significant oxytocin distribution differences across brain regions (F[6; 22] = 2.771, p = 0.0368). The highest oxytocin levels were again found in the hippocampus (left hippocampus: 15.69 ± 3.02 pg/mg of protein, right hippocampus: 15.59 pg/mg of protein). However, multiple pairwise comparisons revealed no statistically significant differences between the studied brain regions (Fig. 1*b*). This indirectly suggests a more uniform oxytocin distribution in the brains of animals that received oxytocin intranasally.

The comparison of oxytocin concentrations between CG and EG mice across brain regions is presented in Figure 2.

Fifteen minutes after oxytocin administration, a clear trend toward increased oxytocin levels was observed in the left olfactory bulb (p = 0.0572). In contrast, oxytocin levels in the right olfactory bulb remained unchanged (Fig. 2).

^{*} Order of the Ministry of Health and Social Development of the Russian Federation No. 708n of August 23, 2010, On the Approval of the Rules of Laboratory Practice. Available at: https://www.garant.ru/products/ipo/prime/ doc/12079613/ (accessed December 5, 2024).

In CG mice, a significant asymmetry in hippocampal oxytocin levels was detected, with higher oxytocin levels in the right hippocampus (p = 0.0192). Following oxytocin administration, its concentration in the left hippocampus increased compared to CG mice receiving saline (p = 0.0223), and this asymmetry was no longer observed (Fig. 2).

In the hypothalamus, oxytocin levels were significantly higher in EG mice than in CG mice (p = 0.0036; Fig. 2).

In contrast, no significant differences in oxytocin levels were found between CG and EG mice in the corpus striatum (Fig. 2).

DISCUSSION

The ability of intranasally administered oxytocin to penetrate the hippocampal region, as demonstrated in

this study, is consistent with findings reported by other researchers. It has been established that in mice, oxytocin administration selectively activates regional cerebral blood flow in the hippocampus [14]. Additionally, direct evidence suggests an increase in oxytocin concentration in the hippocampus and corpus striatum in humans 39-51 minutes after intranasal administration [15, 16]. Furthermore, studies have documented elevated levels of labeled peptides in the striatum of rhesus macaques [17]. However, in our study, intranasal oxytocin administration did not result in significant changes in striatal oxytocin levels (see Fig. 2), despite the relatively low baseline oxytocin concentration in the corpus striatum of CG animals (see Fig. 1a). This suggests that the corpus striatum may be outside the direct pathway of oxytocin penetration into the brain, and a longer post-administration time (beyond



Fig. 1. Oxytocin levels in the mouse brain (pg/mg of protein): *a*, after saline administration; *b*, after oxytocin administration. Notes: "Left", left side of the brain; "Right", right side of the brain. Brain areas assessed: olfactory bulb, hippocampus, hypothalamus, and striatum. In fragment *a*, the bar representing oxytocin concentration in the right hippocampus is highlighted with a bold line and labeled "max". Bar heights represent mean values, with error bars indicating standard error ($M \pm SEM$). Significant differences from oxytocin levels in the right hippocampus: * — *p* < 0.05; ** — *p* < 0.01; *** — *p* < 0.001 (based on ANOVA)

Рис. 1. Уровень окситоцина в головном мозге мышей (пг/мг белка): *a* — после введения физиологического раствора, *b* — после введения окситоцина. Примечания: Лев — левая сторона мозга, Прав — правая сторона мозга; в нижней строке — области мозга, где измеряли уровень окситоцина: об. луковица — обонятельная луковица. На фрагменте *a* жирной линией и надписью «max» выделен столбик, показывающий содержание окситоцина в правом гиппокампе. Высота столбиков соответствует среднему значению, длина вертикального штриха — ошибке среднего (*M* ± *SEM*). Отмечены значимые отличия от содержания окситоцина в правом гиппокампе: * — *p* < 0,05; ** — *p* < 0,01; *** — *p* < 0,001 (по результатам ANOVA)

15 minutes) might have led to an increase in oxytocin levels in the corpus striatum.

A key finding of this study is the importance of considering lateralization when predicting the distribution of administered substances in the brain. Unfortunately, most current research protocols overlook lateral differences, assuming that the brain is bilaterally symmetric by default. Our data indicate that mice exhibit an inherent right-sided asymmetry in hippocampal oxytocin levels, and after symmetrical intranasal instillation, oxytocin levels selectively increase in the left hippocampus. Therefore, the effects of intranasal oxytocin administration may differ fundamentally between left and right homologous brain regions. Previously, we demonstrated that simultaneous oxytocin administration in both nostrils selectively alters monoamine metabolism in only one of the symmetric regions of the forebrain—either on the right or left side [4–6]. Moreover, monoamine metabolism in the left hippocampus (but not the right!) correlates with aggressive behavior: in low-aggression BALB/c mice, it correlates with dopamine turnover, while in highly aggressive outbred white mice, it correlates with serotonin turnover [7].

We propose that intranasal oxytocin administration enhances oxytocin penetration into the left side of the brain, primarily through the left olfactory bulb and hippocampus, ultimately reaching the hypothalamus. These



Fig. 2. Changes in oxytocin levels in different brain regions after intranasal administration of oxytocin. "Left", left side of the brain (dark bars); "Right", right side of the brain (light bars). The hypothalamus (sampled bilaterally) is represented by light gray bars. Groups: "Saline", control mice receiving saline (solid bars); "Oxytocin", experimental mice receiving oxytocin (hatched bars). Bar heights represent mean values, with error bars indicating standard error ($M \pm SEM$). Differences between groups: (*) p = 0.0572 — a trend toward increased oxytocin levels in the left olfactory bulb; * — p < 0.05; ** — p < 0.01; differences between oxytocin levels in the left and right hippocampus: # — p < 0.05 (Student's *t*-test)

Рис. 2. Изменение содержания окситоцина в различных областях головного мозга после интраназального введения окситоцина. Лев — левая сторона мозга (темные столбики), Прав — правая сторона мозга (светлые столбики); гипоталамус, ткань которого забирали билатерально, обозначен светло-серыми столбиками; в нижней строке — группы животных: физ. раствор — мыши контрольной группы, которым вводили физиологический раствор (гладкие столбики); окситоцин — мыши опытной группы, получавшие окситоцин (заштрихованные столбики). Высота столбиков соответствует среднему значению, длина вертикального штриха — ошибке среднего ($M \pm SEM$). Различия между группами: (*) p = 0,0572 — тенденция к возрастанию уровня окситоцина в левой обонятельной луковице; * — p < 0,05; ** — p < 0,01; различия между уровнем окситоцина в левом и правом гиппокампе: # — p < 0,05 (по *t*-критерию Стьюдента) results provide a possible explanation for our previously observed alterations in monoamine metabolism in the left hippocampus following symmetrical intranasal oxytocin administration in mice [4–7].

CONCLUSION

1. Oxytocin distribution in the mouse brain is uneven: the lowest concentration of oxytocin was observed in the hypothalamus, while the highest was in the right hippocampus, indicating an inherent right-sided asymmetry in hippocampal oxytocin levels.

 When oxytocin is simultaneously administered to both nostrils, it predominantly spreads along the left side of the brain, targeting structures of the limbic system, as evidenced by increased concentrations in the left olfactory bulb, left hippocampus, and hypothalamus, but not in the corpus striatum.

3. Research protocols based on the assumption of symmetrical changes in left and right brain regions require reconsideration.

ADDITIONAL INFORMATION

Author contributions. All authors made a significant contribution to the development of the concept, conducting the

study, and preparing the article, read and approved the final version before publication. Contribution of each author: I.V. Karpova data analysis, writing the article; M.V. Litvinova, I.Yu. Tissen, E.R. Bychkov — conducting the experiment; P.D. Shabanov development of the general concept.

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

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