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Fast-Scan Cyclic Voltammetry for Measurement of Extracellular Dopamine Release in Response to Self-Stimulation

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ABSTRACT

BACKGROUND: The regulation of extracellular dopamine levels in the nucleus accumbens is a critical component of the brain reward system. The development of fast-scan cyclic voltammetry facilitated the measurement of variations in dopamine release over time, correlating with behavioral responses. However, the available data on extracellular dopamine levels in response to self-stimulation are somewhat conflicting.

AIM: To analyze the patterns of dopamine release in the nucleus accumbens that occur in response to the ventral tegmental self-stimulation, as measured by fast-scan cyclic voltammetry.

METHODS: Electrodes were implanted into male Wistar rats to induce self-stimulation and monitor extracellular dopamine levels. The release of dopamine was measured telemetrically, while rats were allowed to move freely. Dopamine levels were measured by monitoring its extracellular concentrations in the nucleus accumbens *in vivo* using fast-scan cyclic voltammetry. The ventral tegmental irritation was maintained on a fixed-ratio one schedule using a rectangular pulse train with a 38° head elevation.

RESULTS: The first head elevation, and consequently the activation of reward stimulation, induced an increase in the signal of fast-scan cyclic voltammetry, which decreased over time. The release of dopamine in response to self-stimulation demonstrated a consistent increase compared to the baseline levels prior to the initiation of the reaction training. A definitive correlation between the amplitude/time of dopamine release and the intensity of the self-stimulation response was not observed. The maximum dopamine concentration in response to the electrical stimulus increased and remained at a higher level for at least 20 subsequent head elevations. However, the hallmarks of exploratory behavior persisted, despite variations in dopamine levels. The release of dopamine in the initial five minutes of the experiment gradually decreased every two minutes. Following a period of prolonged self-stimulation, the release of dopamine decreased at an interval of 0.5 min.

CONCLUSION: The study findings are consistent with the hypothesis of fluctuations in the emotional continuum that activates the brain reward mechanisms. Dopamine levels have been demonstrated to reflect the regulatory mechanisms underlying approach and avoidance behaviors in response to self-stimulation and may result from the synthesis of an antedating reward (motivational excitement) followed satisfaction after motor activity.

Keywords: reinforcement; self-stimulation; extracellular dopamine; nucleus accumbens.

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Регистрация высвобождения внеклеточного дофамина при самостимуляции методом циклической вольтамперометрии с быстрым сканированием

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АННОТАЦИЯ

Обоснование. Регуляция внеклеточного уровня дофамина в прилежащем ядре — важное звено механизма внутреннего подкрепления. Развитие метода быстросканирующей циклической вольтамперометрии позволило регистрировать динамику физического выброса дофамина во временной шкале, соответствующей поведенческим реакциям. В то же время данные о внеклеточном уровне дофамина во время реализации реакции самостимуляции в настоящее время противоречивы.

Цель — проанализировать особенности высвобождения дофамина в прилежащем ядре во время самостимуляции вентральной области покрышки методом быстросканирующей циклической вольтамперометрии.

Материалы и методы. Крысам самцам Вистар вживляли электроды для самостимуляции и регистрации внеклеточного уровня дофамина. Регистрацию высвобождения дофамина осуществляли телеметрически у крыс в свободном поведении. Выброс дофамина оценивали по изменению его внеклеточного уровня в прилежащем ядре *in vivo* методом быстросканирующей циклической вольтамперометрии. Раздражение вентральной области покрышки осуществлялось в режиме FR1 пачкой прямоугольных электрических импульсов при подъеме головы на 38°.

Результаты. Первый подъем головы и, соответственно, включение подкрепляющей стимуляции вызывало увеличение сигнала быстросканирующей циклической вольтамперометрии, который уменьшался в течение времени. Высвобождение дофамина при самостимуляции оставалось неизменно выше, чем его фоновый уровень до начала обучения реакции. Мы не наблюдали строгой корреляции величины амплитуды и времени высвобождения дофамина с более или менее энергичной реакцией самостимуляции. Пиковая концентрация дофамина во время электрического стимула увеличивалась и сохранялась на более высоком уровне в течение последующих как минимум 20 подъемов головы. При этом элементы исследовательского поведения не угасали, несмотря на периоды снижения и повышения уровня дофамина. Высвобождение дофамина в первые 5 мин опыта постепенно снижалось каждые 2 мин. После продолжительной самостимуляции высвобождение дофамина снижалось уже каждые 0,5 мин.

Заключение. Наши исследования согласуются с гипотезой флуктуирующего эмоционального континуума, который реализует подкрепляющие механизмы мозга. Уровень дофамина отражает, по-видимому, процессы регуляции механизмов приближения и избегания при самостимуляции и может являться результатом синтеза «опережающего подкрепления» (мотивационного возбуждения) с последующим за двигательным актом состоянием удовлетворения.

Ключевые слова: подкрепление; самостимуляция; внеклеточный дофамин; прилежащее ядро.

Как цитировать

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BACKGROUND

The reinforcement mechanisms underlying the formation of temporal associations in conditioned reflex development and the motivation to earn rewards are, in the words of Pavlov, "the cornerstone of higher nervous activity" [1]. Reinforcement is most closely associated with the dopaminergic mesolimbic system [2]. This system's neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and are involved in the search for and selection of goal-directed behavior aimed at satisfying essential needs [3]. Dopamine (DA) is released from the NAc in response to cues predicting a reward and during the initiation of movement toward a reinforcing stimulus, as well as during VTA stimulation, whereas phasic DA release appears to convey the importance and high likelihood of reward [4].

Thus, phasic DA release enhances reward-related motivational behavior (food or addictive substance) and may lead to its active search [4]. Stimulation of the VTA indeed triggers reward-seeking behavior [5], suggesting that dopaminergic neurons mediate signals related to the anticipated salience of reward. At the same time, the question of how phasic DA release relates to the strength and probability of reinforcement remains largely unexplored.

Intracranial self-stimulation, a process in which animals are trained to self-administer electrical brain stimulation, is used to study the mechanisms of intrinsic reinforcement and has been shown to intensify under the influence of addictive substances and natural rewards [6]. Substances that affect the activity of the dopaminergic system, such as amphetamine, cocaine, and dopamine receptor agonists, increase the intensity of the self-stimulation response [7]. Brain regions where electrical stimulation elicits robust self-stimulation contain dopaminergic neurons [8]. It has been demonstrated that large myelinated descending fibers in the VTA constitute the primary neuronal population activated during electrical self-stimulation [9]. At the same time, individual neurons are thought to activate dopamine cells during intracranial self-stimulation (ICSS) by releasing excitatory neurotransmitters such as glutamate [10]. Dopaminergic neuron activation via optogenetic stimulation has been shown to be sufficient to induce self-stimulation behavior [11].

DA release during self-stimulation was first recorded using microdialysis, which allows for the tracking of gradual changes in its tonic extracellular levels. This method typically demonstrates elevated DA concentrations during self-stimulation, which then return to baseline [12]. The introduction of fast-scan cyclic voltammetry (FSCV) has made it possible to record phasic DA release changes on a timescale that matches behavioral responses [12]. Unlike microdialysis findings, FSCV measurements in the NAc revealed a gradual decrease in DA release during continuous self-stimulation, with no detectable release observed by the end of the experiment [12].

In the present study, we employed the self-stimulation paradigm to investigate its effect on DA release from the NAc using voltammetry in rats. This approach allowed us to quantify how DA release from the NAc is related to intracranial reinforcement induced by electrical stimulation of the dopaminergic neuron region.

This work aimed to analyze the characteristics of DA release in the NAc during VTA self-stimulation.

METHODS

Animal Selection

Six adult male Wistar rats weighing 250–300 g were used. The animals were obtained from the Rappolovo breeding facility (Vsevolozhsky District, Leningrad Region). The rats were housed in standard cages (40×50×20 cm) with ad libitum access to water and pelleted feed in the vivarium of the Institute of Experimental Medicine. Day lighting was used from 08:00 am to 08:00 pm, with ambient temperature maintained at 22±2°C.

All experiments followed the ethical principles outlined in Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010. The study was approved by the Bioethics Committee of the Institute of Experimental Medicine.

Electrode Implantation Surgery

A stimulating electrode (0.2 mm insulated stainless steel bipolar electrode) was implanted into the VTA. The coordinates relative to bregma were: *AP*=–4.9 mm, *L*=0.9 mm, *H*=8.2 mm (Paxinos and Watson, 2005). To record DA level fluctuations in the NAc, a glassy carbon electrode was implanted ipsilaterally (exposed fiber tip: 100 μm in length, 7 μm in diameter). A recording electrode was implanted as follows: *AP*=+1.7 mm (from bregma), *L*=1.8 mm, *H*=7.3 mm from the skull surface (Paxinos and Watson, 2005). Moreover, a 3 mm high-pressure Ag/AgCl reference electrode was implanted: *AP*=+5.5 mm (from bregma), *L*=0. The electrodes were secured to the skull surface with UV-acrylic adhesive. The depths of the stimulating and recording electrodes were adjusted to achieve the maximum signal corresponding to DA release, and the electrodes were then secured in place. The animals were subsequently housed in individual cages.

Experiments on Self-Stimulation Response

For this study, we developed a hardware-software system that measures DA release using FSCV during electrical stimulation of the brain reward area. The experiment was carried out using the Cyclone telemetry-based hardware-software system, which includes

several modules: an FSCV unit (potentiostat), an electrical stimulator (neural tissue stimulator), visual and auditory stimulators, an accelerometer to determine head position, and a video tracking module for monitoring the animal's position [13–15].

The experiments on the self-stimulation response were conducted in a circular chamber (outer diameter 50 cm, inner diameter 26 cm). The number of 38° head elevations and the self-stimulation response threshold (in μA) were recorded over a 10-minute session. Self-stimulation was performed in the FR1 mode, with each head elevation reinforced by electrical stimulation of the VTA (rectangular pulse, 1 ms, 100 Hz, for 0.5 s). To determine the stimulation threshold, current was applied in 2 μA increments, 5 seconds each, in a forced mode until clear head elevation responses were observed. The current intensity was then increased by 50% of the threshold and subsequently decreased (in 2 μA increments, 5 seconds each) until head elevation responses disappeared [13]. The optimal current intensity for eliciting self-stimulation was selected during testing.

Dopamine Release Recording

DA release was recorded telemetrically in freely moving rats during the self-stimulation procedure. DA release was assessed by measuring changes in its extracellular levels in the nucleus accumbens *in vivo* using FSCV [16]. Stimulation of the VTA was triggered by head elevation movements and delivered as a train of rectangular electrical pulses (current intensity 50% above the self-stimulation threshold, pulse duration 1 ms, frequency 100 Hz, for 1 s).

To record increases in DA levels in response to VTA stimulation, a holding potential of –0.4 V and a scan duration of 9 ms were used. Scanning pulses were applied every 100 ms. The anodic limit was +1.3 V. For data analysis, the open-source web application Analysis Kid was used. Analysis Kid developed by Hashemi Lab (USA) enables visualization, calibration, and filtering of neurochemical signals [17].

Morphological Control of Electrode Positioning

At the end of the experiments, the rats were sacrificed by ethaminal sodium overdose and perfused with 0.9% sodium chloride solution. The brain was then extracted, embedded in celloidin, sectioned coronally, and stained with cresyl violet using the Nissl method (Fig. 1). Electrode positioning was verified after the end of the experiments using histological brain sections and a stereotaxic atlas [21]. To confirm the position of the stimulating electrode in the VTA, a coronal section was made at the "Bregma –5.3 mm" level according to the stereotaxic atlas. In this brain region, the VTA tissue is at its most extensive and corresponds to the dopaminergic paranigral nucleus. To confirm the position of the electrode in the nucleus accumbens, a coronal section was made at the "Bregma +2.7 mm" level according to the atlas. Sectioning continued for 0.7–1 mm to the region of the forebrain where the nucleus accumbens occupies the largest area (Fig. 1). In this region of the brain, the anterior commissure was displaced toward the dorsomedial portion of the nucleus, whereas the recording electrode tract was located in its largest, central region (Fig. 1).

Statistical Analysis

The obtained data were statistically processed using GraphPad Prism 8.1 (GraphPad Software, USA). The D'Agostino–Pearson test was used to assess the normality of the distribution of random variables, and the data were then presented as median and quartiles [Q_1, *Me*, Q_3]. Data analysis was performed using the Kruskal–Wallis test, followed by Dunn's multiple comparison test. Differences were considered significant at $p < 0.05$.

RESULTS

Monitoring of Behavior and Extracellular Dopamine Levels

Self-stimulation was tested in the FR1 mode, with each head elevation reinforced by electrical stimulation of the VTA. Brain stimulation during head elevation activated VTA neurons via an electrode, whereas a carbon fiber microelectrode was implanted in the NAc to record changes in DA levels using FSCV (Fig. 2). Electrical stimulation (1 ms pulses, 100 Hz, for 0.5 s) produced a stable self-stimulation response exceeding 20 head elevations per minute in the fixed-ratio FR1 mode with continuous reinforcement. The rats continued to engage in intensive sniffing (exploratory behaviors) despite periodic increases in head elevation frequency and decreases in received stimulations. To assess whether DA release correlated with head elevation behavior, we tracked DA release from the NAc during ICSS in the FR1 mode (n=20 sessions, 6 rats).

Behavioral and FSCV findings for representative animals are shown in Figs. 3 and 4. The first head elevation, and thus the initiation of reinforcement stimulation, elicited an immediate increase in the FSCV signal, which then declined over time. We assessed the amplitude of individual DA release events triggered by self-stimulation, with intervals between stimulations associated with rearing with sniffing or head tilts below 38° during the session. Self-stimulation-evoked DA release remained above baseline levels observed prior to the initiation of self-stimulation training (p=0.001) (Fig. 3). To assess whether changes in response strength or the interval between stimulations were associated with DA release, the animals were subjected to increasing current intensity at a fixed ratio during individual self-stimulation sessions. At the same time, we found no correlation between the

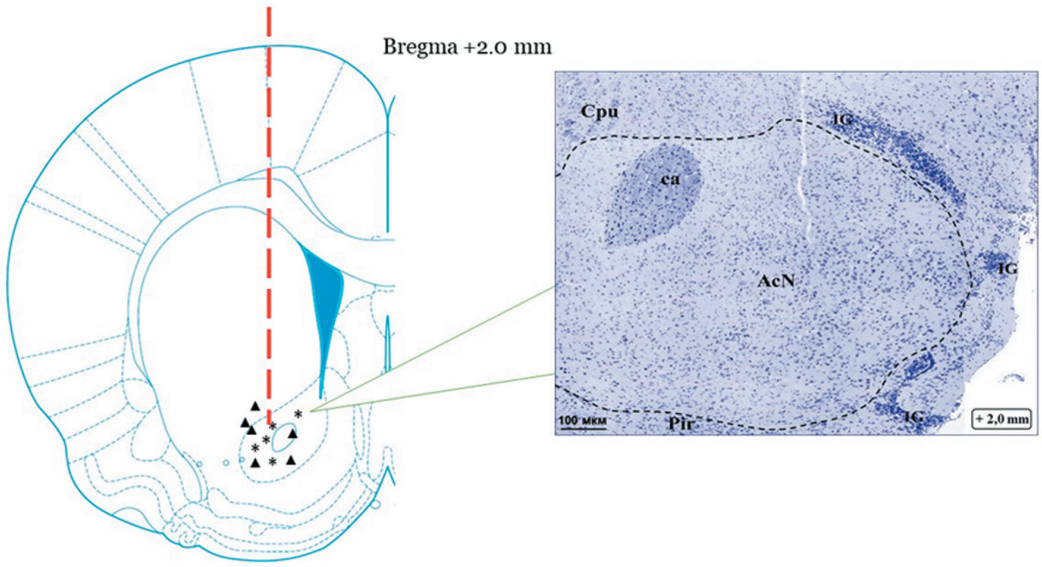

Fig. 1. Morphological monitoring of the electrode implantation site in the brain. Left panel, mapping of the measurement points in the nucleus accumbens. Right panel, anterior nucleus accumbens with a brain defect associated with the electrode implantation at Bregma +2.0 level. AcN, nucleus accumbens; ca, anterior commissure (inside the nucleus); Cpu, corpus striatum; IC, olfactory nuclei; Pir, piriform cortex (adjacent nuclei). Cresyl violet Nissl staining. Eye lens ×10, objective lens ×10.
Рис. 1. Морфологический контроль локализации электродов в головном мозге крыс. Слева — картирование исследованных точек регистрации AcN. Справа — передняя часть AcN (прилежащего ядра) с дефектом мозга из области вживления электрода для регистрации на уровне «Bregma +2,0». AcN — прилежащее ядро; ca — передняя спайка мозга (расположена внутри ядра); Cpu — полосатое тело; IC — обонятельные ядра; Pir — грушевидная кора (сопредельные нервные центры). Окраска крезиловым фиолетовым по методу Ниссля. Ок. ×10, об. ×10.

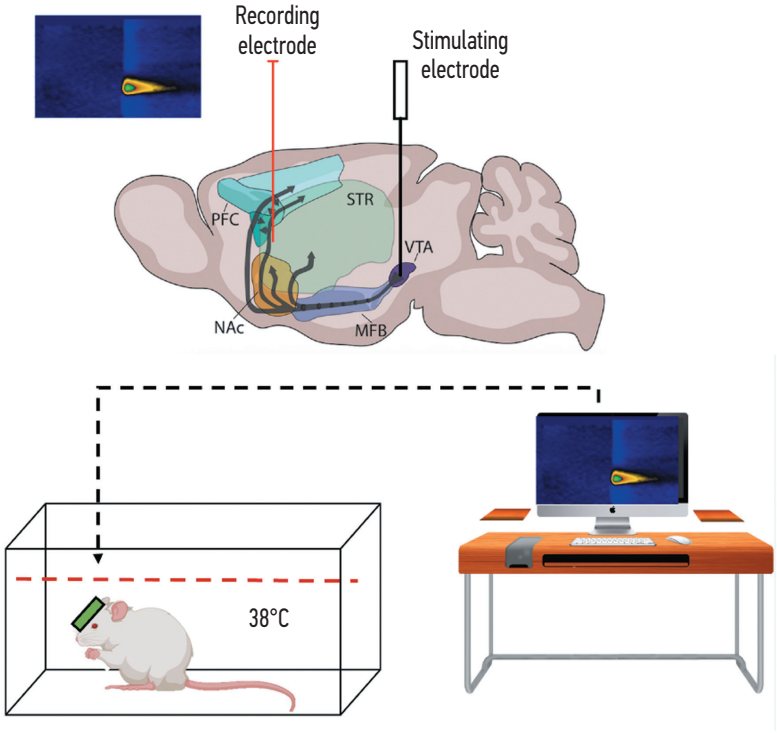

Fig. 2. Training of the self-stimulation response to head elevation and measurement of extracellular dopamine levels. PFC, medial prefrontal cortex; STR, corpus striatum; VTA, ventral tegmental area; MFB, medial forebrain bundle; NAc, nucleus accumbens.
Рис. 2. Обучение реакции самостимуляции при подъеме головы и регистрация внеклеточного уровня дофамина. PFC — медиальная префронтальная кора; STR — полосатое тело; VTA — вентральная область покрышки; MFB — медиальный передний мозговой пучок; NAc — прилежащее ядро.

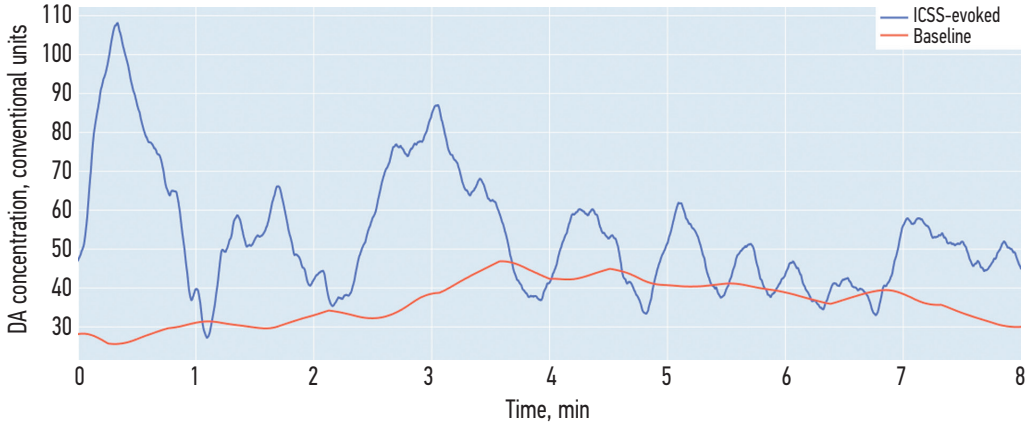

Fig. 3. Dopamine release in response to self-stimulation in the 10-min experiment. A shift in dopamine levels was observed in response to self-stimulation (blue curve) and prior to the training of self-stimulation reaction (red curve). An illustrative figure of an animal is presented. ICSS, intracerebral self-stimulation.

Рис. 3. Высвобождение дофамина при самостимуляции за 10 мин опыта. Показано изменение уровня дофамина (nA) при самостимуляции (синяя кривая) и изменение уровня дофамина до обучения реакции самостимуляции (красная кривая). Показан пример животного. ICSS — внутримозговая самостимуляция.

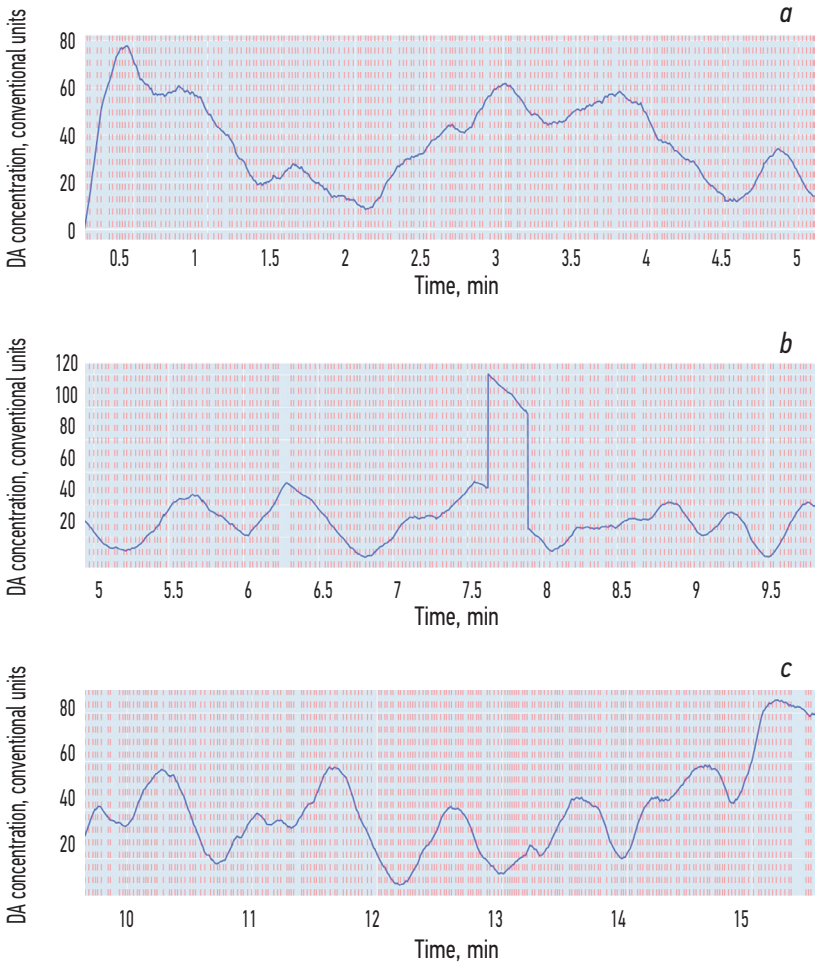

Fig. 4. Variation in dopamine levels in response to self-stimulation: *a*, variation in dopamine levels within the first five minutes of the self-stimulation experiment; *b*, variation in dopamine levels between the fifth and tenth minutes of the self-stimulation experiment; *c*, variation in dopamine levels between the tenth and fifteenth minutes of the self-stimulation experiment. Individual self-stimulation reactions (head elevation) are indicated by vertical hatching lines. An illustrative figure of an animal is presented.

Рис. 4. Динамика уровня дофамина (nA) при самостимуляции: *a* — изменение уровня дофамина в течение первых 5 мин опыта по самостимуляции; *b* — изменение уровня дофамина с 5-й по 10-ю минуту опыта по самостимуляции; *c* — изменение уровня дофамина с 10-й по 15-ю минуту опыта по самостимуляции. Отдельные реакции самостимуляции (подъем головы) показаны вертикальной штриховкой. Показан пример животного.

amplitude and timing of DA release and a more or less vigorous self-stimulation response.

Dopamine Release During Self-Stimulation

To assess whether phasic DA activation is indeed sufficient to trigger exploratory behavior elements in rats (such as locomotion with sniffing and rearing with sniffing), the animals' behavior was monitored in a circular chamber (Fig. 4). Exploratory behavior and dopamine release were observed during self-stimulation. The peak concentration of DA during stimulation gradually increased and remained elevated over the course of at least 20 subsequent head elevations. At the same time, despite periods of both decrease and increase in DA levels, exploratory behavior components such as sniffing, locomotion with sniffing, and rearing with sniffing did not diminish. Despite constant stimulation parameters and sufficient self-stimulation intensity, DA release gradually decreased every 2 minutes during the first 5 minutes of the experiment. After prolonged self-stimulation, it began to decrease every 0.5 minutes, subsequently returning to baseline high levels during the session (Fig. 4). DA release in response to stimulation remained stable over the course of three consecutive sessions. Taken together, these results indicate that phasic DA activation in the VTA is sufficient for intensive self-stimulation and induces elements of exploratory behavior (Fig. 4).

Dopamine Release and Evaluation of the Reinforcing Properties of Stimulation

To assess whether the information associated with phasic activation of the region containing DA neurons correlates with concomitant behavioral changes evoked by stimulation and DA release in the NAc, we analyzed the moments of VTA electrical stimulation and corresponding DA release in the NAc over a one-minute interval. When analyzing the correlation between dopamine level changes and individual head elevation responses

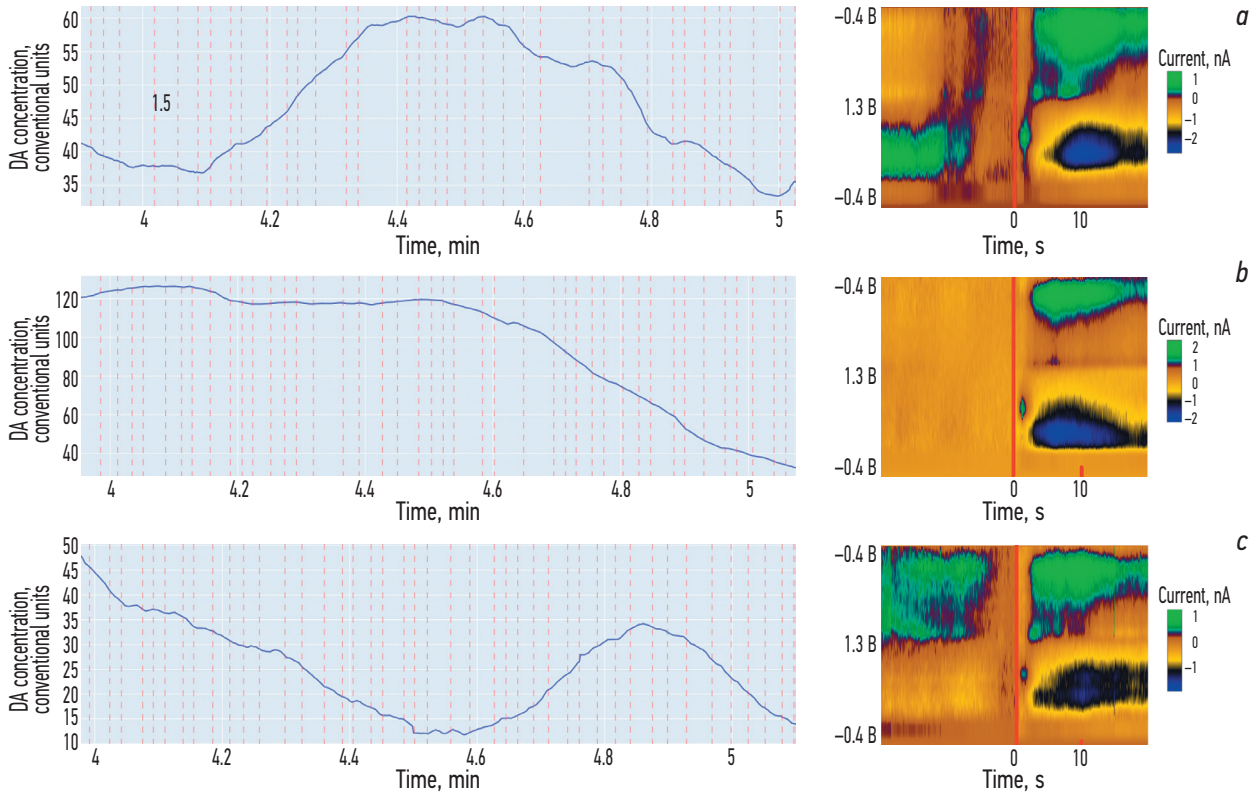

Fig. 5. Comparative analysis of variations in dopamine levels and individual reactions of head elevations in response to self-stimulation: *a*, variation in dopamine levels within a 1-minute interval (from the fourth to the fifth minute) of the self-stimulation experiment and respective voltamogram recorded during ventral tegmental stimulation. The color scale represents electric current variations measured in the nucleus accumbens relative to its baseline level at time point 0. The vertical lines demonstrate the times at which the rats elevated their heads, thus indicating the activation of electrical ventral tegmental stimulation. *b*, *c*, variations in dopamine levels within a 1-minute interval (from the fourth to the fifth minute) of the self-stimulation experiment in other rats.

Рис. 5. Анализ сопоставления изменений уровня дофамина (nA) с отдельными реакциями подъемов головы животного при самостимуляции: *a* — изменение уровня дофамина в течение 1 мин (с 4-й по 5-ю минуту) опыта по самостимуляции и соответствующую этому периоду опыта вольтамперограмму при стимуляции VTA. Цветовая шкала отражает величину изменения электрического тока при регистрации его в NAc по сравнению с его уровнем в точке 0 по оси времени. Вертикальными линиями показаны моменты подъема головы и соответственно включение электрической стимуляции VTA; *b*, *c* — изменение уровня дофамина в течение 1 мин (с 4-й по 5-ю минуту) опыта по самостимуляции у других крыс.

during self-stimulation, we examined DA level fluctuations over a one-minute interval (from the fourth to the fifth minute) of the self-stimulation session and superimposed the voltammogram corresponding to this period of the experiment (Fig. 5). For this analysis, we evaluated the color scale that represented changes in electric current recorded in the NAc relative to baseline at the zero point on the time axis. Individual VTA stimulations corresponding to head elevation responses were identified on the color scale. It was found that stimulation-evoked DA release in the NAc does not necessarily reflect an expected or experienced decrease in perceived reward value due to increased effort (head elevation during intracranial reinforcement) or temporal assessments (time required for stimulation). Furthermore, in these specific experimental conditions, stimulation-evoked DA release in the NAc did not predict the latency of the learned instrumental response. The amount of DA released during the experiment did not differ significantly depending on the intensity of self-stimulation.

DISCUSSION

In the present study, we attempted to demonstrate the relationship between DA release and VTA activation during self-stimulation by recording changes in phasic DA release in the nucleus accumbens using FSCV. We used a constant current intensity 1.5 times higher than the self-stimulation threshold and a fixed pulse frequency (100 Hz). This approach allowed us to capture changes in phasic DA release on a timescale corresponding to behavioral responses. Electrical stimulation produced a stable self-stimulation response exceeding 20 head elevations per minute in the fixed-ratio FR1 mode with continuous reinforcement. This raises the question of whether self-stimulation and phasic DA release are linked. Despite a robust self-stimulation response, we observed both increases and decreases in DA release during self-stimulation. We also observed periodic increases and decreases in the number of head elevations (number of received stimulations). The animals continued to engage in intensive sniffing behaviors (exploratory behaviors), regardless of changes in DA levels or head elevation frequency. The first head elevation (triggering the reinforcing stimulation) elicited an increase in the FSCV signal, which then declined or plateaued as the session progressed. At the same time, DA release induced by self-stimulation consistently remained higher than baseline phasic DA release prior to the initiation of self-stimulation training.

Thus, this study demonstrated that DA release in the NAc occurs both at the initiation and during the self-stimulation response, with a decline observed toward the end of the session (Fig. 3). Moreover, given the rate at which releasable DA pools are replenished, the inhibition of DA release mediated by autoreceptors [16], and the rapid reuptake of DA, which is likely enhanced during repeated depolarization [17], it is reasonable to expect DA levels in the NAc to become dependent on neuronal activation during self-stimulation. We found that DA release, time-locked to each stimulation, occurred throughout the entire session and was closely associated with behavioral responses (Figs. 4, 5).

In the present study, we analyzed changes in DA release in the NAc during self-stimulation. It was shown that exploratory behavior components in rats did not diminish despite periods of decreasing and increasing DA levels. Despite constant stimulation parameters and sufficient self-stimulation intensity, DA release gradually decreased every 2 minutes during the first 5 minutes of the experiment and returned to baseline high levels. After prolonged self-stimulation, DA release declined every 0.5 minutes and also returned to baseline high levels during the session (Fig. 4), without fading over time. Previous studies using microdialysis demonstrated increased DA concentrations during self-stimulation, which then returned to baseline [12].

Other studies found no DA release during the subsequent, prolonged phases of the response [18]. Earlier studies using FSCV showed that DA release in the NAc does not occur during ICSS [19]. These findings led to the conclusion that DA release in the NAc may be important for signaling the presence or predictability of rewards, but is not associated with ongoing reinforcement [15]. However, optogenetic studies have confirmed that activation of DA neurons in the VTA is sufficient to support reinforcement [20], which is suppressed by the administration of DA receptor antagonists in the NAc [21]. Thus, there are currently conflicting data regarding the presence of DA release and its characteristics during self-stimulation.

Our findings support the hypothesis of a fluctuating emotional continuum that underlies the brain's reinforcement mechanisms during self-stimulation [22]. The analysis performed in this study, comparing DA level fluctuations with individual head elevation responses during self-stimulation and evaluating changes in DA levels throughout the self-stimulation session, allowed us to compare the curve of phasic DA release with the proposed fluctuating emotional continuum [23]. DA levels gradually decreased and returned to baseline, apparently reflecting internal reinforcement regulation during self-stimulation. The reinforcement level as a current emotional state may result from both "anticipatory reinforcement" (motivational arousal prior to receiving electrical stimulation, reflecting the appetitive phase) and satisfaction that follows the motor act, reflecting the consummatory phase of behavior [24]. Despite constant stimulation parameters and sufficient self-stimulation intensity, the number of head elevations increased and

decreased intermittently, apparently reflecting reward valuation processes in the regulation of approach and avoidance behaviors. Previous studies have shown that increasing the duration or number of imposed stimulations in the positive reinforcement zone may lead to avoidance behavior [2]. Therefore, the animal regulates the extent of emotionally driven reinforcement by increasing or decreasing self-stimulation frequency. This is primarily reflected by extracellular DA levels. The circumplex model of affect, based on the bivalent system of pleasure-displeasure and arousal-inhibition, is the best model for explaining our data on emotional regulation during self-stimulation [23, 24].

CONCLUSION

Thus, our findings indicate that DA release is associated with the animal's regulation of the reinforcing emotional effect during self-stimulation.

ADDITIONAL INFO

Authors' contributions. N.S. Pestereva: conducted experiments, wrote and edited the manuscript; D.S. Traktirov: performed statistical analysis, edited the manuscript; A.A. Lebedev, S.S. Pyurveev: wrote and edited the manuscript, conceptualized the study; R.D. Cherkassova: conducted experiments; P.D. Shabanov: wrote and edited the manuscript. The authors have approved the version for publication and have also agreed to be responsible for all aspects of the work, ensuring that issues relating to the accuracy and integrity of any part of it are properly considered and addressed.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Н.С. Пестерева — проведение экспериментов, написание и редактирование текста статьи; Д.С. Трактиров — проведение статистического анализа, редактирование теста статьи; А.А. Лебедев, С.С. Пюрвеев — написание и редактирование текста статьи, концепция исследования; Р.Д. Черкассова — проведение экспериментов; П.Д. Шабанов — написание и редактирование текста статьи. Авторы одобрили версию для публикации, а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

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Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

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