Research Article

Apelin-13 regulates electrical activity in the globus pallidus and induces postural changes in rats

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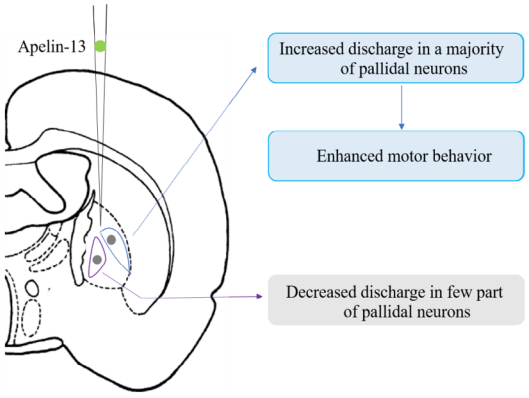
Graphical Abstract *Effects of electrophysiology and motor behavior on apelin-13 in the globus pallidus*



Abstract

The globus pallidus is the relay nucleus of the basal ganglia, and changes in its electrical activity can cause motor impairment. Apelin-13 is widely distributed in the central and peripheral nervous systems. It has been demonstrated that apelin-13 plays important roles in the regulation of blood pressure and other non-motor functions. However, its role in motor function has rarely been reported. In the present study, apelin-13 (10 μM/100 μM) was injected into the globus pallidus of rats. The results showed that apelin-13 increased the spontaneous discharges in the majority of pallidal neurons. However, an apelin-13-induced inhibitory effect on the firing rate was also observed in a few pallidal neurons. In postural tests, after the systemic administration of haloperidol, unilateral pallidal injection of apelin-13 caused a contralateral deflection. Together, these findings suggest that apelin-13 regulates the electrical activity of pallidal neurons and thus participates in central motor control in rats. The study was approved by the Animal Ethics Committee of Qingdao University (approval No. 20200615Wistar0451003020) on June 15, 2020.

Key Words: apelin-13; basal ganglion; electrophysiology; firing rate; globus pallidus; microinjection; motor behavior; movement disorder

Chinese Library Classification No. R453; R338.8; R363

Introduction

Apelin was first purified from bovine stomach in 1998 (Tatemoto et al., 1998). It originates from a 77-amino-acid precursor, preproapelin, which is divided into several molecular forms, including apelin-12, -13, -17, and -36 (Hosoya et al., 2000; Lee et al., 2000; Langelaan et al., 2009; Antushevich and Wójcik, 2018). Apelin exerts its diverse functions, such as the regulation of water and food intake (Taheri et al., 2002; Sunter et al., 2003; Clarke et al., 2009), blood pressure (Yamaleyeva et al., 2016), pituitary hormone release (Taheri et al., 2002; Newson et al., 2009), oxidative stress (Foroughi et al., 2019; Zhu et al., 2020), and apoptosis and autophagy (Pouresmaeili-Babaki et al., 2018; Foroughi et al., 2019; Zhu et al., 2020), through the apelin receptor (APJ). APJ belongs to the G protein-linked receptor family. Apelin and APJ exist in both the periphery and brain in human and rodents, including in the kidney, liver, cortex, thalamus, hippocampus, and basal ganglia (O'Dowd et al., 1993; Choe et al., 2000; De Mota et al., 2000; Hosoya et al., 2000; O'Carroll et al., 2000).

The globus pallidus (GP) in rodents is a relay nucleus of the basal ganglia. Recently, Crompe et al. (2020) highlighted the crucial role of the GP in firing rate and synchronized oscillatory activity across cortico-basal ganglia circuits. In addition, studies have revealed the vital role of the GP in movement control. For example, unilateral lesions of the GP induce ipsilateral turning, while unilateral activation leads to contralateral turning in rats (Ossowska et al., 1983; Ossowska and Wolfarth, 1995). Moreover, optogenetic stimulation of pallidal neurons produces hyperkinesia in transgenic mice (Tian et al., 2018). Additionally, in primates, administration of bicuculline (a γ-aminobutyric acid type A receptor antagonist) into the GP generates abnormal movement (Grabli et al., 2004). However, although there is a large amount of evidence that apelin participates in the control of non-movement functions, the effects of apelin on central motor control

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remain unclear. In the present study, we aimed to investigate whether the application of apelin-13 into the GP modulates electrical activity and/or motor function in rats.

Materials and Methods

Animals

Adult Wistar rats (specific-pathogen free, aged 8–10 weeks, weighing 240–280 g) were purchased from Ji Nan Peng Yue Animal Ltd. (license No. SCXK (Lu) 2019-0003) for the present study. To exclude the effects of estrogen on spontaneous firing in female rats, only male rats were included in this study. Rats had free access to food and water and were housed in the Animal Center of Qingdao University. In the feeding room, the lights were turned on at 8:00 and turned off at 20:00. Rats were raised in groups of four in the home cage at a suitable room temperature (22 ± 1°C). The rats were acclimated for at least 5 days before the experiment began. All surgical procedures were performed in a way that minimized the suffering of the animals, and the number of rats used in the experiment was reduced as much as possible. The animal experiment was approved by the Animal Ethics Committee of Qingdao University (approval No. 20200615Wistar0451003020) on June 15, 2020. The rats were randomly divided into saline (n = 6), 10 μM apelin-13 (n = 9), and 100 μM apelin-13 (n = 10) groups in the electrophysiological experiment, and saline (n = 6) and 10 μM apelin-13 (n = 10) groups in the postural test.

In vivo electrophysiological recordings

Urethane (Shanghai Macklin Biochemical Co., Ltd., Shanghai, China) was used to anesthetize the rats (1 g/kg, intraperitoneal injection). If the rats began to awaken during long recordings, 0.16 g/kg urethane was applied to maintain the anesthesia. The coordinates of the GP (0.80–1.20 mm posterior, 2.50–3.50 mm lateral from the bregma) for the craniotomy were based on the stereotaxic atlas (Paxinos and Watson, 2007). Multi-barrel glass microelectrodes (Nanjing Rantai Teaching Equipment Factory, Nanjing, China) with one recording electrode and two microinjection barrels were used in the experiment, as described in our previous study (Xue et al., 2016). A pressure injector (four-channel, PM2000B, MicroData Instrument, Inc., Plainfield, NJ, USA) was connected to two barrels filled with different drugs: either 0.9% normal saline or 10 μM apelin-13 (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA). The prepared electrodes were then placed stereotaxically into the GP. According to the location (identified after the experiment) and the electrophysiological characteristics of pallidal neurons, drugs were then ejected onto pallidal neurons through the machine using pulse gas pressure of between 5.0 and 15.0 psi (34.47–103.42 kPa), after 10 minutes of stable recording.

A microelectrode amplifier (Cat# 1700; A-M Systems, Sequim, WA, USA) was used to amplify the recorded electrical signals. These signals were filtered through a pass filter (low-pass filter, 5000 Hz; high-pass filter, 1 Hz). Electrical data, including discharge rate, coefficient of variation (CV), and Fano factor (FF), were analyzed online using Spike 2 software (Cambridge Electronic Design Limited, Cambridge, UK), and were later also analyzed offline (Wang et al., 2019b). The firing parameters, including firing rate, CV, and FF, under basal conditions were considered using the average discharge of 120 seconds of data before saline or apelin treatment (Xue et al., 2016; Wang et al., 2019a; Taylan and Bariskaner, 2020). The peak response in frequency within 50 seconds following normal saline or apelin-13 treatment was identified as the effects of the drug. A change in firing parameters exceeding two standard deviations (SDs) was regarded as significantly different.

Postural test

The rats used for the postural test were not the same as those used for electrophysiological recordings. Two guide cannulae (outside diameter, 0.5 mm; inner diameter, 0.4 mm) were embedded into the bilateral GP of each rat. To fix the cannulae in place, screws (RWD Life Science Co., Ltd., Shenzhen, China) and dental acrylic were applied to the skull. To eliminate the possible effects of impairments induced by surgery, guide cannulae were placed on both sides. The free-moving rats were then placed in a cage to acclimate to the new situation for at least 10 minutes. Haloperidol (Sigma-Aldrich, Darmstadt, Germany; 0.25 mg/kg, intraperitoneal injection) was then used to induce akinesia in the awake rats by blocking dopamine D2 receptors. After 10 minutes, normal saline or 10 μM apelin-13 was microinjected into the GP unilaterally through the cannula (0.1 μL/min, 0.5 μL). The hemisphere to be microinjected with drugs was decided randomly. After the microinjection of saline or apelin, we took photos to measure the postural asymmetry of rats. We opened the photos using PowerPoint (Microsoft Corporation, Redmond, WA, USA) and drew the nose–back and back–tail lines onto each photo. Finally, we used a protractor to measure the postural asymmetry angle on the screen and calculate the postural asymmetry score. Postural asymmetry scores were defined as 1 (below 30°); 2 (30°–59°); 3 (60°–89°); or 4 (90° or more) (Miwa et al., 2000). This postural test was performed in a blinded manner; one person performed the microinjection of drug or vehicle into the GP and took the photos, and another person (with no knowledge of the materials injected into the GP of each animal) measured the asymmetry data on the computer. Histological controls were performed after the electrophysiological experiments and postural tests. The rats were perfused and the brains were removed and sectioned at 50 μm. All rats were verified after the experiments. Rats were only analyzed if the location of their microinjection cannula was correct.

Statistical analysis

Data are expressed as the mean ± standard error of the mean (SEM). SPSS 22.0 software (IBM, Armonk, NY, USA) was used for data analysis. The paired t-test was performed to compare the spontaneous discharge parameters before and after saline or apelin-13 treatment. The chi-squared test was used to compare the percentage of apelin-13-responsive neurons between the 10 μM and 100 μM apelin-13 groups. The Mann–Whitney U test was used to compare the increased or decreased proportion of firing between the saline and apelin-13 groups, as well as the postural asymmetry scores. P-values of less than 0.05 were considered to be statistically significant.

Results

Apelin-13 modulates the discharge frequency of pallidal neurons

In total, 66 pallidal neurons were recorded from 25 rats, and two to four pallidal neurons with spontaneous firing were usually successfully obtained per rat. Three firing patterns—regular (**Figure 1A**), irregular (**Figure 1B**), and bursting (**Figure 1C**)—were detected in these pallidal neurons. Thirty-seven pallidal neurons were recorded in the 10 μM apelin-13 group. The firing rate was increased in 24 neurons after microinjection of 10 μM apelin-13, from 11.68 ± 1.22 Hz to 14.54 ± 1.39 Hz (t = –8.209, P < 0.001, **Figure 2A** and **C**). The percentage of excitatory effects induced by apelin-13 (average increase: 28.90 ± 3.67%) was significantly increased (z = –4.371, P < 0.001) compared with that induced by saline treatment (average change: 1.24 ± 1.01%; basal: 12.47 ± 1.33 Hz; saline: 12.65 ± 1.39 Hz; n = 11, t = –1.131, P = 0.284, **Figure 2C**). However, in seven neurons, the firing rate was decreased after the application of apelin-13, from 8.19 ± 2.14 Hz to 6.04 ± 1.75 Hz (t = 3.605, P = 0.011, average decrease: 29.04 ± 4.95%, **Figure 2B** and **C**). The application of apelin-13 had no effect in the remaining six pallidal neurons (basal: 12.29 ± 2.06 Hz, apelin-13: 12.07 ± 2.38 Hz, t = 0.314, P =

0.766). Further analysis revealed that apelin-13 treatment had no significant effect on the CV (basal: 0.46 ± 0.05; apelin-13: 0.63 ± 0.12; n = 31, t = –1.654, P = 0.109) or FF (basal: 0.10 ± 0.03; apelin-13: 0.25 ± 0.14; n = 31, t = –1.128, P = 0.268) of apelin-13-responsive neurons.

A higher concentration (100 μM) of apelin-13 was then used to observe whether apelin-13 at higher concentrations still induced bidirectional effects on the discharge activity of pallidal neurons. The firing rate was increased by 100 μM apelin-13 in 10 out of 18 pallidal neurons, from 11.21 ± 1.46 Hz to 13.55 ± 1.39 Hz (t = –8.833, P < 0.001, average increase: 27.93 ± 7.24%). Furthermore, apelin-13 at 100 μM decreased the spontaneous discharge rate in seven of the 18 neurons, from 7.45 ± 2.01 Hz to 5.75 ± 1.91 Hz (t = 9.210, P < 0.001, average decrease: 33.65 ± 8.11%). The firing rate was unchanged in the remaining pallidal neuron. The CV and FF were also unchanged after apelin-13 administration (data not shown). Between the 10 μM and 100 μM groups, the apelin-13-induced increases (28.90 ± 3.67% and 27.93 ± 7.24%, respectively) and decreases (29.04 ± 4.95% and 33.65 ± 8.11%, respectively) in firing rates were not significantly different (P > 0.05). The percentage of apelin-13-responsive neurons in the 100 μM group (17/18, 94.4%) tended to be higher than that of the 10 μM group (31/37, 83.8%); this was especially apparent in the apelin-13-induced inhibitory neurons (100 μM: 38.9%; 10 μM: 18.9%).

Postural effects of unilateral administration of apelin-13 into the GP

The present electrophysiological results indicated that apelin-13 exerts excitatory effects in the majority of pallidal neurons. Previous studies have demonstrated that the electrical activity of pallidal neurons is closely related to motor behavior (DeLong, 1971; Gardiner and Kitai, 1992; Hegeman et al., 2016; Wang et al., 2019b). We therefore investigated whether a microinjection of apelin-13 into the GP was able to modulate postural behavior in awake rats. It is known that any direct injection into the tissue may generate oxidative stress, thus affecting experimental results because of reactive oxygen species production. Therefore, normal saline was administered as a control, to eliminate the impact of reactive oxygen species on the results of both the electrophysiological and postural studies.

In the present postural tests, haloperidol was used to produce akinesia and catalepsy in awake rats (Cui et al., 2007). Unilateral microinjection of normal saline into the GP did not induce any fixed postural asymmetry in six rats. However, after the unilateral administration of 10 μM apelin-13 into the GP, a contralateral deflection posture appeared almost immediately in the 10 rats who received this treatment. Apelin-13 induced significant contralateral dystonic posture at 20 minutes (P = 0.033), 30 minutes (P = 0.009), 50 minutes (P = 0.019), and 60 minutes (P = 0.005) after apelin-13 injection compared with the control group (**Figure 3**).

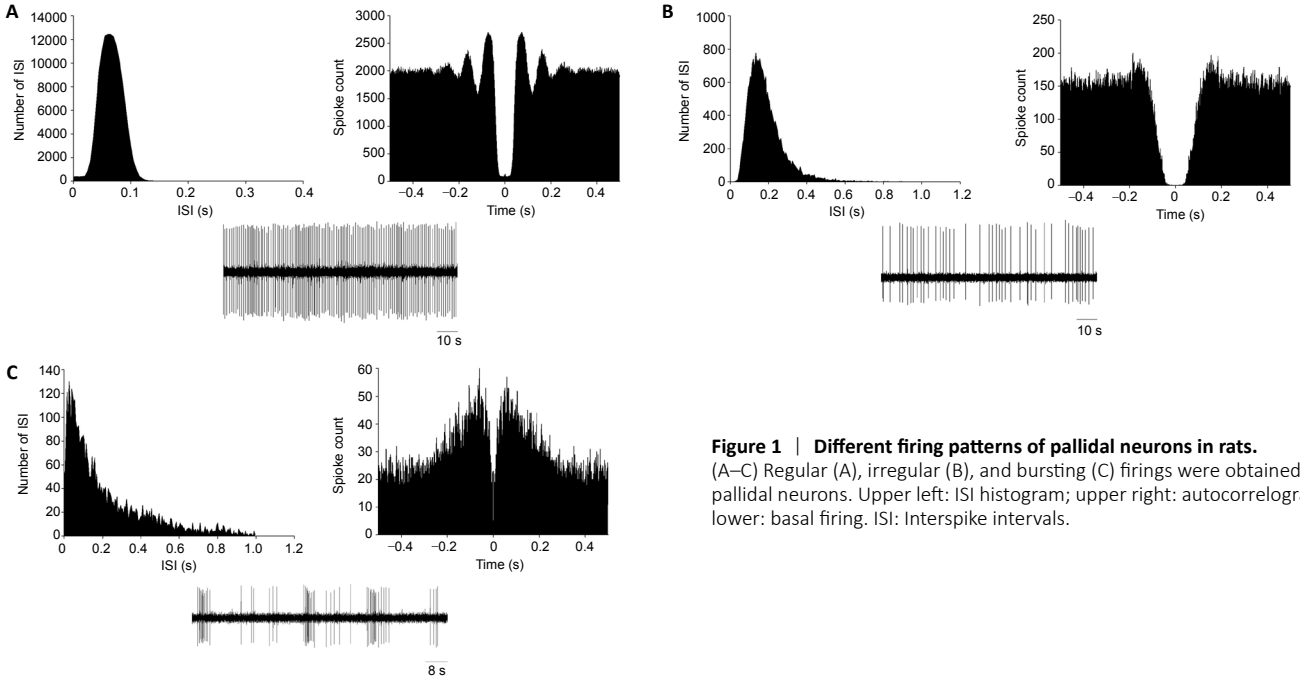

Figure 1 | **Different firing patterns of pallidal neurons in rats.**
(A–C) Regular (A), irregular (B), and bursting (C) firings were obtained from pallidal neurons. Upper left: ISI histogram; upper right: autocorrelogram; lower: basal firing. ISI: Interspike intervals.

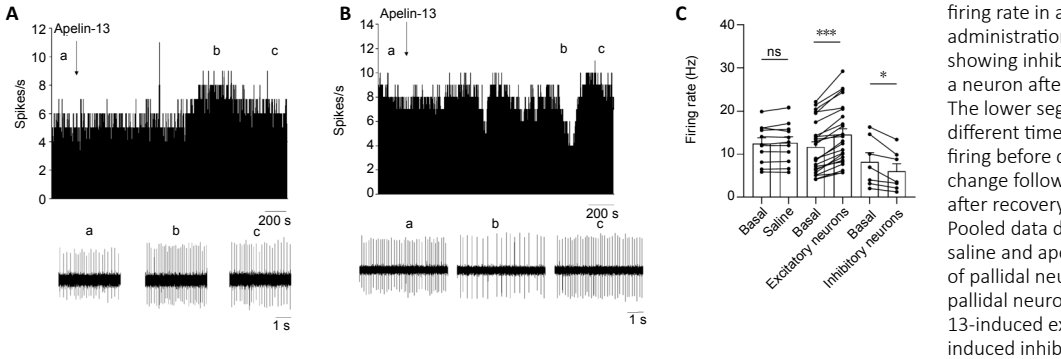

Figure 2 | **Effects of 10 μM apelin-13 on the discharge rate of pallidal neurons in rats.**
(A) Frequency histograms displaying an increased firing rate in a neuron after 10 μM apelin-13 administration. (B) Typical frequency histograms showing inhibition of the discharge frequency of a neuron after 10 μM apelin-13 administration. The lower segments (a, b, and c) are from three different time phases of the experiment. a: Stable firing before drug application; b: the maximal change following drug application; c: stable firing after recovery from the drug application. (C) Pooled data demonstrating the effects of normal saline and apelin-13 on the discharge frequency of pallidal neurons. The numbers of recorded pallidal neurons in the saline group, apelin-13-induced excitatory neurons, and apelin-13-induced inhibitory neurons were 11, 24, and 7, respectively. Data are expressed as the mean ± SEM. *P < 0.05, ***P < 0.001 (paired t-test). ns: Not significant.

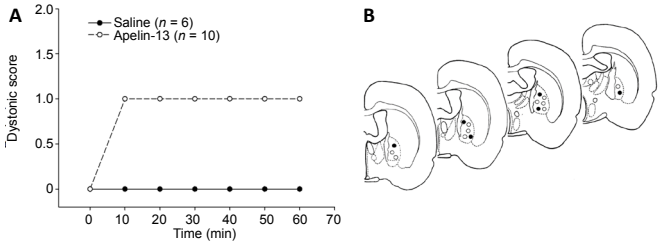

Figure 3 | **Effects of apelin-13 injection in the GP on postural behavior in rats.**

(A) Postural data demonstrating that unilateral intrapallidal injection of 10 μM apelin-13 induced contralateral dystonic posture in rats receiving haloperidol. Data are represented as median values, and were analyzed using the Mann–Whitney *U* test. (B) Verification of the correct position of microinjection in the GP. GP: globus pallidus.

Discussion

Apelin-13 exerts excitatory or inhibitory effects on the discharge of pallidal neurons

Although there is very little immunohistochemical evidence of the expression of APJ receptors in the brain, the present electrophysiological study demonstrated that apelin-13 modulates the firing of pallidal neurons. It has been previously reported that apelins regulate the electrical activity of neurons in several brain regions. For example, apelin-13 depolarizes proopiomelanocortin neurons through the phospholipase C signaling pathway (Lee et al., 2015). Apelin-13 depolarizes the membrane potential and excites vasopressin neurons, but does not change the electrophysiological activity of oxytocin neurons (Tobin et al., 2008). In contrast, in lactating animals, intracerebroventricular administration of apelin-17 decreases the phasic electrical activity of vasopressin neurons (De Mota et al., 2004). Furthermore, Dai et al. (2013) revealed that apelin-13 modulates the excitability of subfornical organ neurons by generating either depolarizing or hyperpolarizing responses. Similarly, the present electrophysiological results revealed a dual effect of apelin-13 on the discharge of pallidal neurons at concentrations of both 10 μM and 100 μM. Apelin-13 induced excitatory effects in the majority of pallidal neurons, whereas it induced inhibitory effects in a small number of neurons. There seemed to be a higher percentage of apelin-13-responsive neurons at higher concentrations (100 μM) of the drug than at lower concentrations (10 μM). A possible explanation for the bidirectional apelin-13-induced effects on the discharge of pallidal neurons may be as follows. First, there are two major types of pallidal neurons: parvalbumin-positive and neuronal PAS domain protein 1 (NPAS1)-positive neurons. These are classified according to specific characteristics and make up 55% and 27%, respectively, of all pallidal neurons (Hernández et al., 2015; Hegeman et al., 2016; Pamukcu et al., 2020). Parvalbumin-positive neurons are high-frequency firing neurons with projections mainly to the subthalamic nucleus, while NPAS-positive neurons are low-frequency firing neurons with targets in the dorsal striatum (Abecassis et al., 2020). In the electrophysiological recordings of the present study, the basal firing rate of apelin-13-induced excitatory pallidal neurons (10 μM: 11.68 ± 1.22 Hz; 100 μM: 11.21 ± 1.46 Hz) seemed to be higher than that of apelin-13-induced inhibitory neurons (10 μM: 8.19 ± 2.14 Hz; 100 μM: 7.45 ± 2.01 Hz). We thus speculate that the apelin-13-induced excitatory or inhibitory effects may be related to the different types of pallidal neurons. Electrophysiological recordings in brain slices may help to identify the subtypes of pallidal neurons, and therefore add novelty to the present work. However, technical limitations meant that we were unable to accurately recognize the types of recorded pallidal neurons in the current study. A previous study has demonstrated that different ionic mechanisms are involved in the apelin-13-induced bidirectional electrophysiological effects in the subfornical organ (Dai et al., 2013). In this region, apelin-13 depolarizes neurons by activating a non-selective cationic conductance, while it hyperpolarizes neurons by activating a potassium conductance (Dai et al., 2013). Therefore, further *in vitro* electrophysiological experiments, including patch-clamp recordings, may be necessary to identify the mechanisms of apelins on the different types of pallidal neurons.

Apelin-13 in the GP enhances motor function in rats

It is well known that apelins have an important and broad range of functions, including that of motor control in the central nervous system. For example, intracerebroventricular administration of apelin-13 induces a significant activation of locomotion (Jászberényi et al., 2004). In addition, the GP has important roles in motor regulation under both healthy and diseased conditions. In our previous research, the activation of GP neurons was demonstrated to enhance motor behavior in normal rats (Cui et al., 2007; Xue et al., 2016). Haloperidol blocks dopamine D2 receptors, thus increasing the activity of striatal medium spiny neurons that project to the GP. The resulting hypoactivity of pallidal neurons and reduced γ-aminobutyric acid release then induce the excessive inhibition of thalamocortical activity, leading to akinesia. Under haloperidol administration, drugs that increase the activity of GP are likely to compensate for the haloperidol-induced hypoactivity of the GP, thus causing different activity between the intact and drug-administered sides. The results of the present postural test revealed that unilateral injection into the GP of apelin-13 induced a contralateral dystonic posture, which suggests that apelin-13 treatment ameliorates the haloperidol-induced hypoactivity of the GP, and in turn facilitates motor output in the ipsilateral cortex. A recent study revealed that different types of pallidal neurons may be differently engaged in regulating motor behavior (Pamukcu et al., 2020). Optogenetic stimulation of parvalbumin-positive neurons enhances movement in naïve mice, while NPAS1-positive neurons are considered to inhibit movement (Pamukcu et al., 2020). Based on the results of the present study, we hypothesize that pallidal apelin-13 treatment likely enhances movement through complex effects on different types of neurons.

Conclusion

Intrapallidal application of apelin-13 regulates the spontaneous firing activity of pallidal neurons. Our results suggest that pallidal apelin-13 enhances motor behavior mainly through excitatory effects on GP neurons. Because the present study revealed that apelin-13 only increased the firing rate in some pallidal neurons, further study is necessary to recognize the types of neurons that are affected by apelin-13, and to detect the accurate effects of apelin-13 in the GP.

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