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The role of septal somatostatin neurons in stress

외측 중격 소마토스타틴 뉴런의 스트레스 상황에서의 역할

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서울대학교 대학원

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Abstract

The role of septal somatostatin neurons in stress

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Stress, as a disruption of homeostasis, induces diverse behaviors and autonomic responses, but the underlying neural circuit mechanism remains unclear. Here I provide evidence that neurons in the dorsal lateral septum (LSd) that express the somatostatin gene (hereafter, LSd^{Sst} neurons) respond to the stressor, and are involved in reducing heart rate of stressed mice. I performed in vivo fiber photometry recording from LSd^{Sst} neurons and revealed that this neural population is activated by stressor. Chemogenetic inhibition of LSd^{Sst} neurons decreases the heart rate of stressed mice. Optogenetic stimulation of LSd^{Sst} neurons, however, did not affect both stress-related behaviors

and autonomic responses. Together, these results imply that under stressful circumstances, LSd^{Sst} neurons are activated and play a role in cardiac activity.

keywords : stress, heart rate, somatostatin, lateral septum

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Introduction

Stress—generally referred to as a disruption of homeostasis—affects a wide range of behavioral and physiological factors, from the heart and breathing patterns to arousal and emotional states (Chrousos & Gold, 1992; de Kloet et al., 2005; Hollon et al., 2015; Koob, 2008; Lupien et al., 2009; McEwen, 2004; Ulrich-Lai & Herman, 2009; Winsky-Sommerer et al., 2005). Although adaptive stress responses are necessary for the survival and well-being of all animals, excessive and unfavorable stress responses contribute to the etiology of many illnesses, including anorexia, depression, and anxiety disorder (Chrousos, 2009; de Kloet et al., 2005; Hardaway et al., 2015; Nestler et al., 2002; VanItallie, 2002; Yaribeygi et al., 2017). As a result, a lot of workhave been done to figure out the mechanisms underlying the stress responses, which is still an active area of research (Yang et al., 2018; Cui et al., 2018; Bhatnagar, 2021; Ahn et al., 2022; Cathomas et al., 2019; Sanacora et al., 2022; Hu et al., 2020; S.-R. Kim & Kim, 2021; Fenster et al., 2018; Parekh et al., 2022).

The lateral septum (LS) is a forebrain structure that regulates emotional behaviors, stress-related behaviors, and autonomic

responses and therefore is well-positioned to mediate stress-induced alterations in behavior and physiology (Anthony et al., 2014; Azevedo et al., 2020; Bakshi et al., 2007; Besnard et al., 2019; Leroy et al., 2018; Mu et al., 2020; Reis et al., 2011a; Shin et al., 2018; Singewald et al., 2011; C. Wang & Kotz, 2002; Wong et al., 2016; Xu et al., 2019). For example, a previous study showed that increased blood pressure by immobilization stress was inhibited by injecting the gamma-aminobutyric acid receptor agonist in the ventral LS (Kubo et al., 2002). Also, local microinjection of non-selective synapse blocker in the LS reduces mean arterial pressure and heart rate during restraint stress (Reis et al., 2011). LS also mediates the baroreflex, the mechanism of maintaining the constant heart rate (Scopinho et al., 2007). Besides the role of autonomic response, LS neurons have behavioral functions in stressful circumstances. For instance, the subset of LS neurons that expresses type 2 corticotropin-releasing factor receptors mediate stress-induced anxiety-like behaviors through the anterior hypothalamic nucleus (AHN) (Anthony et al., 2014). In addition, LS neurons that express dopamine receptor 3 are downregulated after early social deprivation, and this neural population mediates stress-induced social dysfunctions (Shin et al., 2018). However, the molecular identity of LS neurons that mediates autonomic responses to stress is still largely unknown.

The LS is a heterogeneous region consisting of many distinct subregions and cell types implicated in diverse functions (Azevedo et al., 2020; Besnard et al., 2019). Among them, current research has emphasized the function of the dorsal part of the LS (LSd) in stress-related behaviors (Azevedo et al., 2019; Carus-Cadavieco et al., 2017; Risold & Swanson, 1997b, 1997a; Sweeney & Yang, 2015, 2017; Terrill et al., 2016, 2018), where the neurons expressing the somatostatin gene (*Sst*) are concentrated (Köhler & Eriksson, 1984; Risold & Swanson, 1997a; Sheehan et al., 2004). The LSd has been implicated in mediating a variety of stress responses (Besnard et al., 2019; Leroy et al., 2018; Wong et al., 2016) and strongly projects to the anterior hypothalamus (AH), which mediates stress-induced anxiety and cardiac activity (Anthony et al., 2014).

Based on these findings, here I tested the correlative and causal functions of LSd^{Sst} neurons in autonomic responses and stress-related behaviors using in vivo fiber photometry, chemogenetic inhibition, and optogenetic stimulation. I hope my study helps the understanding of the role of LSd^{Sst} neurons in stressful circumstances.

Materials and Methods[1)]

Mice

The Seoul National University Institutional Animal Care and Use Committee approved all procedures. Adult wild-type (WT) or heterozygote mice from C57BL/6J background (C57BL/6J mice, JAX #000664; $Sst^{tm2.1(cre)Zjh}$/J, JAX #013044) were housed at a temperature- and humidity-controlled environment with a reverse 12-hour light/dark cycle, with ad libitum access to food and water. During the dark cycle, all behavior tests were performed. Data were collected from male and female mice at least six weeks old. I combined data from males and females because no indication of sex differences was identified in any of my experiments.

Viral constructs

The recombinant adeno-associated virus (AAV) vector expressing GCaMP6m (AAV1-hSyn-FLEX-GCaMP6m, 1.2×10^{13} copies/ml) was obtained from the Penn Vector Core, and the AAVs expressing channelrhodopsin (AAV5-EF1α-DIO-hChR2(H134R)-eYFP, 6.2×10^{12} copies/ml) was obtained from the UNC vector core. The AAV vectors expressing hM4Di (AAV9-hSyn-DIO-hM4D(Gi)-mCherry, 2.5×10^{13} copies/ml) were obtained from Addgene.

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1) This section is based on an unpublished paper (An et al., 2022).

Stereotaxic surgery

Mice were given 1.5–3.0% isoflurane anesthesia and placed in a stereotaxic device (David Kopf Instruments) while resting on a heating pad. Following a scalp incision, a minor craniotomy was done at the regions of interest with a hand drill. A pressure injection apparatus (Nanoliter 2000) with a drawn glass capillary was used to inject between 250 and 300nl of viral vectors into the LS at a rate of 50 nl/min. To prevent the virus from flowing backward, the capillary was slowly retracted after injection. The coordinates were +1.00 mm antero-posterior (AP), ±1.2 mm medio-lateral (ML), -2.70 mm dorso-ventral (DV) at -18 degrees for LSd stimulation and inhibition, except for the fiber photometry group. A custom-made stainless steel bar (4.0×1.0×1.0mm3) was affixed to the dental cement for head fixation during the surgery.

For fiber photometry recordings from the LSd, recombinant AAVs expressing GCaMP6m were unilaterally injected into the LSd of $Sst^{cre/+}$ mice at -18 degree angle relative to the sagittal plane at +1.00 mm AP, -0.44 mm ML, -2.79 mm DV to avoid the lateral ventricles. Then a low-autofluorescence fiberoptic cannula (Doric Lenses, NA 0.48, 400 μm core) was implanted 50 μm above the virus injection site in the same manner. The cannulae were attached to the skull with C&B metabond (Parkell) and dental cement.

For optogenetic stimulation experiments, recombinant AAVs expressing channelrhodopsin (ChR2) were injected into the LSd of *Sst*$^{cre/+}$ mice. For stimulation experiments, fiberoptic cannulae (NA 0.22, 200 μm core) were bilaterally implanted. The coordinates for cannulae were +1.00 mm AP, ±1.2 mm ML, -2.70 mm DV with an 18-degree angle to bilateral injection into a small site.

For chemogenetic inhibition experiments, AAVs expressing hM4Di were injected into the LSd of *Sst*$^{Cre/+}$ mice. For control cohorts of the LSd experiments, wild type mice were injected with the AAV expressing hM4Di.

The incision was sutured and mice were provided with antibiotics and analgesics. Mice were kept in their home cage for 4 weeks for recovery and sufficient viral expression.

Fiber photometry

Fiber photometry recordings were performed as previously described. Briefly, excitation lights from 470-nm and 405-nm LEDs (Thorlabs, M470F3/M405F1) that were sinusoidally modulated by the RZ5P processor (Tucker Davis Technologies) at 211 Hz and 531 Hz, respectively, were delivered to the target region of mice via a low-autofluorescence fiberoptic patch cord and cannula (Doric Lenses, 400 μm-core, 0.48 NA). Throughout the recordings, a maximum of 20 μW of light was kept on. A

femtowatt photoreceiver (Newport, 2151) detected the emitted fluorescence. The RZ5P processor demodulated, amplified, and collected the resulting signal at ~1 kHz. Behavioral experiments were recorded using a video camera, and the location and activity of the mice were automatically measured by video tracking software (Noldus Ethovision) to correlate the photometry signals with behavior. A TTL pulse generated by a pulse generator (Sanworks, Pulse Pal) was split and fed into the RZ5P processor. A TTL-triggered blue LED was placed in the field of view where mice could not see. For the tail restraint, event timestamps marking restraint deliveries were used.

Optogenetic and chemogenetic manipulations

For optogenetic stimulations, 8~10 mW blue light (159 mW/mm^2 at the tip of the patch cords) was generated by a 473-nm laser (MBL-III-473; OEM Laser Systems) and delivered to mice through fiberoptic patch cords (0.22 NA, 200 μm diameter; Newdoon) connected by a rotary joint (Doric Lenses). Light pulses (10ms pulse trains at 15 Hz) were generated by controlling the blue laser with a pulse generator (Pulse Pal, Sanworks).

For chemogenetic inhibition, 200ul of 0.9% saline or CNO (HB6149; Hellobio) was administered intraperitoneally into mice 45 before the behavioral test session (4 mM, prepared in 0.9% sterile saline). In the case of chemogenetic inhibition of

stress-induced anxiety test, I administered saline or CNO 15 minutes before 20 minutes of restraint stress.

Behavioral assays

Before behavior experiments, all mice were handled for at least three days to reduce the anxiety effect by me. Prior to fiber photometry and optogenetics experiments, mice were connected to a patchcord for five minutes before being introduced to the behavior arena. For all behavior assays, in which video analysis was appropriate, video tracking software (Noldus, EthoVision XT) was used to track the location and activity of mice. For tail restraint and social behavior tests, experiments are recorded and analyzed manually.

For the elevated plus maze (EPM) test, mice were placed in a plus-shaped plastic maze. The maze consists of two open and closed arms (30 × 5 cm) extending from a central platform elevated 50cm above the floor. The behavior of each mouse was observed for 10 minutes after being placed in closed arms.

For the tail restraint test, Mice were put into an open field (25 × 25 × 25 cm) and freely moved for the first 5 min and then I grabbed the tail and slightly sustained for five times. To prevent the predictive effect of this stress, randomly (but, equally in all experiment sessions, 2 min on average) grab the tail.

For the open field test (OFT), mice were placed in an open field chamber (50 × 50 × 50 cm), where the center zone was defined as a square at the center (25 × 25 cm). Each mouse was placed at the corner at the beginning of the session. Mouse behavior was recorded for 10 min for the inhibition experiment. For stimulation experiments, mice were recorded for 9 min, in which laser stimulation was applied at the second 3-min epochs; the two laser-off and one laser-on epochs were pooled for analysis (off-on-off).

For the social behavior test, a subjective mouse was placed in their home cage, and an intruder mouse was introduced in the cage for 10 min.

In the stress-induced anxiety test, mice were placed in a transparent Plexiglas tube with an inner diameter of 3 centimeters, and two caps with holes for the nose and tail were fitted to hold the mice tightly. For 20 minutes. After 20 minute restraint, mice were released and transferred to a new cage in the testing room for 5 minutes, then subjected to an OFT or EPM.

Data Analysis

All data were analyzed with custom-written Matlab (Mathworks) code. The photometry signal was analyzed as previously described (Jung et al., 2022; D.-Y. Kim et al., 2020). Briefly, data were low-pass filtered at 2 Hz, downsampled to 100 Hz, and a linear function scaled the 405-nm signal to the 470-nm signal to obtain the fitted 405-nm signal. The ΔF/F was calculated as (raw 470 nm signal – fitted 405 nm signal) / (fitted 405 nm signal). Peri-event time plots were created using timestamps marked by manual video analysis.

Histology and Microscopy

To verify the viral expression and placement of the optic fiber, I conducted perfusion and obtained brains. Mice were fully anesthetized by isoflurane and transcardially perfused by PBS and 4% paraformaldehyde. Obtained brins were additionally fixed for a day and moved to PBS-based 30% sucrose solution. Archived brains in a 4'c refrigerator was cut into 50um-thick sections using a freezing microtome (Leica, SM2010R). For nucleus staining, sliced brain samples were washed out by PBS and incubated in 1:25000 DAPI (4',6-diamidino-2-phenylindole) solution for 30 min. Before the brain samples were mounted on a slide glass with PVA-DABCO, the brain samples were washed out again by PBS for 10 min, 3 times. The samples are imaged using a confocal microscope (Zeiss LSM 880).

Statistical Analysis

Statistical analyses and linear regressions were performed using Matlab (Mathworks) or Prism (GraphPad). I used a two-tailed Wilcoxon rank-sum test, one-way repeated measures ANOVA, two-way repeated-measures ANOVA with subsequent Bonferroni post-tests, or Pearson correlation depending on the experimental paradigm. $*p<0.05$, $**p<0.01$, $***p<0.001$. Data were presented as mean ± s.e.m. unless otherwise noted. No statistics to determine sample size, blinding, or randomization methods were used. Viral expression and implant placement were verified by histology before mice were included in the analysis.

Results

1. LSd^{Sst} neurons are activated in response to tail restraint stress

To measure the activity of LSd^{Sst} neurons neurons in response to stress in vivo, I injected Cre-inducible AAV vectors carrying calcium reporter GCaMP6 in the LSd of *Sst*$^{Cre/+}$ mice and implanted a fiberoptic cannula above the injection site. After four weeks, I performed fiber photometry recordings during the tail restraint stress (Figures 1A). After 5 min of habituation, I grabbed the tail of a freely moving mouse five times for 10 sec. As a result, I found that LSd^{Sst} neurons were activated in response to tail restraint stress in a time-locked manner. The activity of LSd^{Sst} neurons reached a peak level right after the tail was grabbed (Figures 1B, C, D). From this result, I found that LSd^{Sst} neurons are activated in a stressful circumstance.

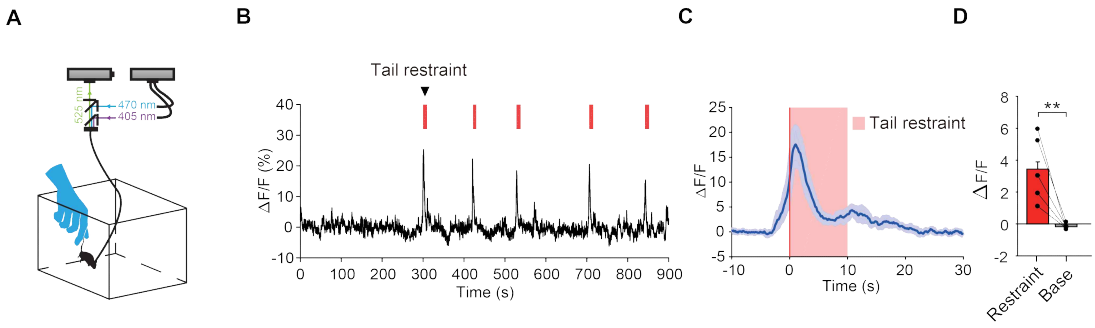

Figure 1. LSd^{Sst} neurons are activated in response to tail restraint stress (A) Schematic of the fiber photometry system. (B) LSd^{Sst} neurons were activated by tail restraint (C) Average calcium transients around the tail restraint time showed time-locked responses of LSd^{Sst} neurons (n = 5). Shaded box, tail restraint. (D) Average normalized calcium responses of LSd^{Sst} neurons during tail restraint were larger than the activity level during the rest of the session (Base) (n = 5, p = 0.008). Data were represented as mean ± s.e.m. Asterisks indicate significance levels for comparisons in each panel obtained by Wilcoxon rank-sum test (**p < 0.01).

2. Inhibiting LSd^{Sst} neurons reduces heart rate in stressed mice

I then asked if LSd^{Sst} neurons are required for autonomic stress responses. To explore the autonomic effect of inhibiting LSd^{Sst} neurons in a stressful situation, I Cre-dependently expressed hM4Di in the LSd of *Sst*$^{cre/+}$ mice. The LSd^{Sst} neurons are inhibited by intraperitoneal (i.p.) injection of clozapine *N*-oxide (CNO). On the test day, I measured the heart rate and respiratory rate in the head-fixed mice after the CNO or saline injection. Notably, I found that inhibition of LSd^{Sst} neurons reduced heart rate while did not affect the respiratory rate(Figures 2A, B, E, F). CNO administration in control mice not expressing the Cre-dependent hM4Di did not affect the heart and respiratory rate. Since head-fixation without enough habituation can cause stress to animals (Juczewski et al., 2020), I speculated that the LSd^{Sst} neurons have a role in regulating the heart rate under the a stressful situation. Indeed, head-fixed mice showed a higher heart rate (710~792 bpm) than the normal resting heart rate (500~700bpm) (Janssen et al., 2016). Together, these results suggest that the LSd^{Sst} neurons are involved in regulating the heart rate in stressed mice.

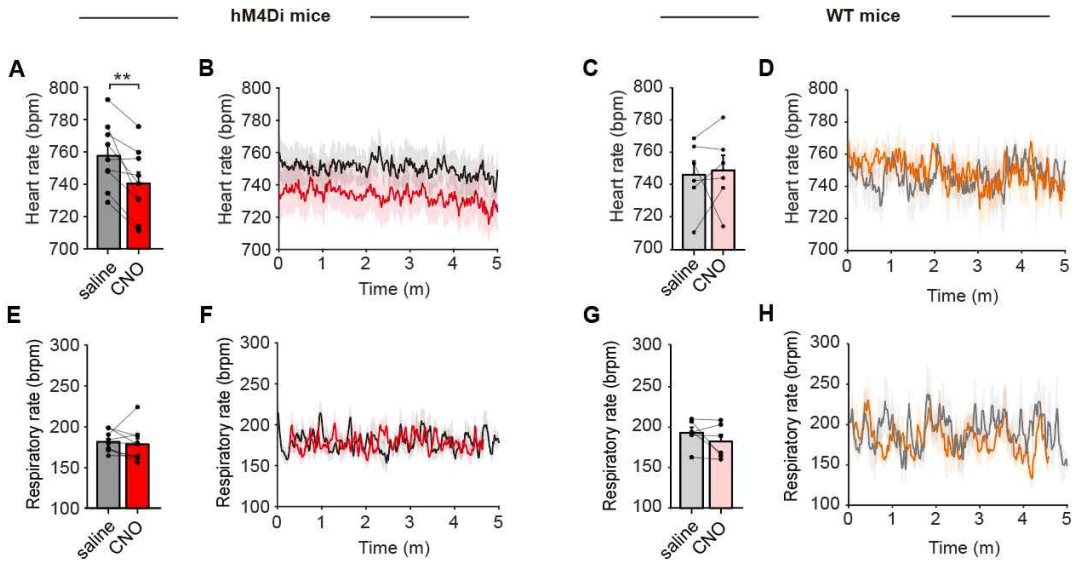

Figure 2. Inhibition of LSd^{Sst} neurons decreased heart rate but did not affect the respiratory rate in stress in head-fixed mice. (A, B) The injection of CNO in mice that express hM4Di reduced heart rate. (n =9, p = 0.007). (C, D) The injection of CNO in WT mice that do not express hM4Di did not alter heart rate. (n =6, p = 0.688). (E, F) The injection of CNO in mice that express hM4Di did not alter respiratory rate (n =9, p = 0.359). (G, H) The injection of CNO in control mice that did not express hM4Di did not alter respiratory rate. (n = 6, p = 0.219).

3. Inhibiting LSd^{Sst} neurons did not affect stress-related behaviors

Since anxiety-like behaviors are related to stress state (Anthony et al., 2014; Crumeyrolle-Arias et al., 2014), I also conducted stress-induced anxiety-like behavior tests to see if the LSd^{Sst} neurons have a role in anxiety-like behavior in stressful situations. To elevate the stress level of mice in behavior tests, mice were exposed to a custom-designed restraint tube for 20 min, 5 min before the test session. The velocity of mice was not affected by the inhibition of the LSd^{Sst} neurons in both OFT and EPM. Time spent in the center zone of OFT or open arms of EPM, an anxiogenic environment for mice was also not affected by the inhibition of LSd^{Sst} neurons. Inhibition of the LSd^{Sst} neurons did not affect frequency or latency to the center zone of OFT or open arms of EPM as it did on time in the center or open arms.

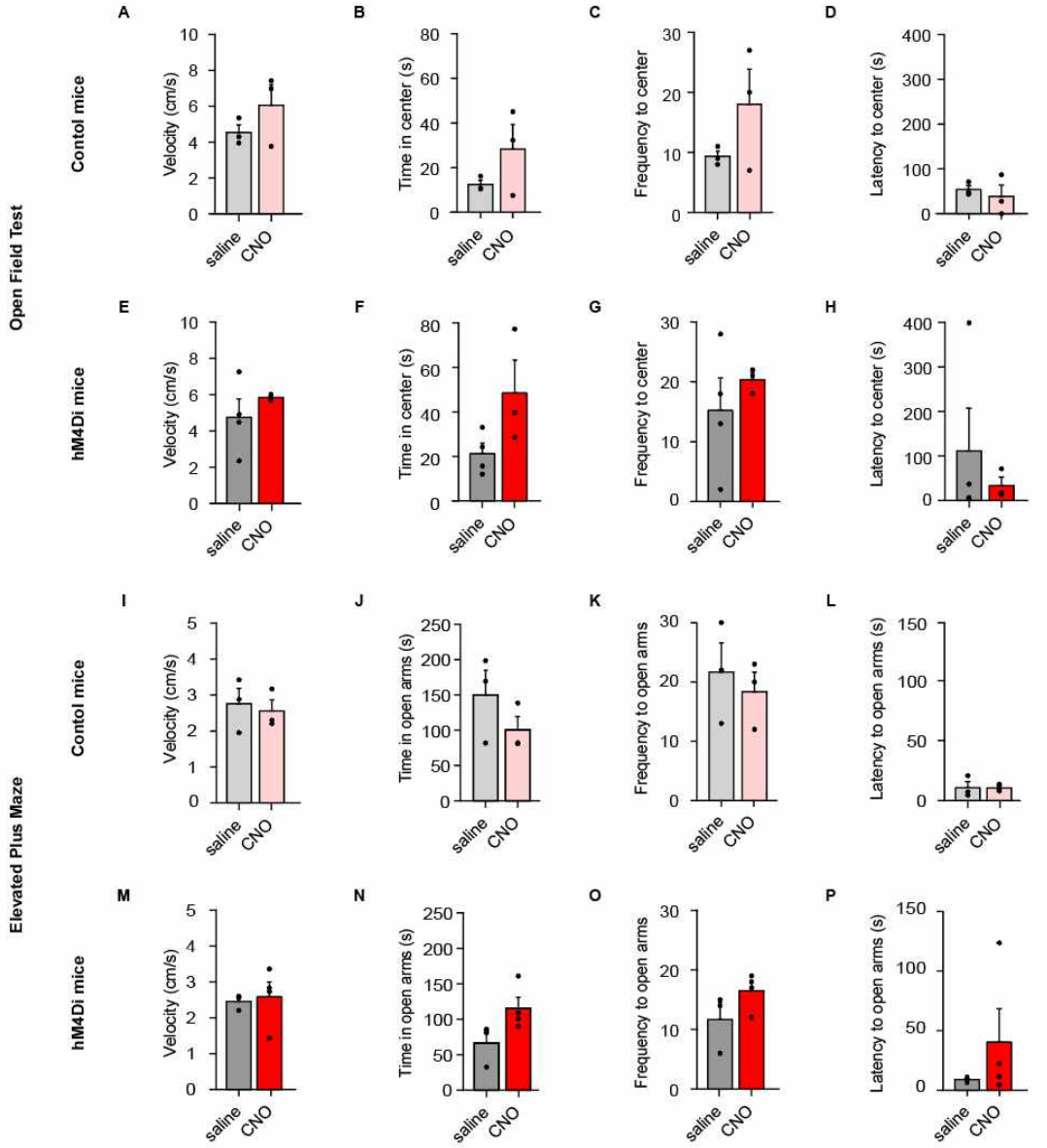

Figure 3. Inhibition of LSd^{Sst} neurons did not affect stress-induced anxiety. (A-H) In OFT, chemogenetic inhibition of LSd^{Sst} neurons did not affect locomotion and time spent, frequency and latency to the center of both WT and hM4Di mice (n = 3 Ctrl + saline, n = 3 Ctrl + CNO, p = 0.700 (A), p = 0.700 (B), p = 0.700 (C), p =

0.700 (D), n = 4 hM4Di + saline, n = 3 hM4Di + CNO, p = 0.400 (E), p = 0.114 (F), p = 0.457 (G), p = 0.857 (H)). (I-P) In EPM, chemogenetic inhibition of LSd^{Sst} neurons did not affect locomotion and time spent, frequency and latency to the open arms of both hM4Di and WT mice (n = 3 Ctrl + saline, n = 3 Ctrl + CNO, p > 0.999 (I), p = 0.400 (J), p = 0.800 (K), p = 0.700 (L), n = 3 hM4Di + saline, n = 4 hm4Di + CNO, p = 0.400 (M), p = 0.0571 (N), p = 0.400 (O), p = 0.400 (P)).

4. Activating LSd^{Sst} neurons did not affect stress-related autonomic responses

To test if activating LSd^{Sst} neurons can induce autonomic responses to stress, I measured the heart rate and the respiratory rate during optogenetically activating LSd^{Sst} neurons. Optogenetic stimulation of LSd^{Sst} neurons, however, neither altered the heart rate nor respiratory rate (Figures 4A-E). One explainable hypothesis is that the LSd^{Sst} neurons may be already highly activated during the measurements because of the stress caused by head-fixation.

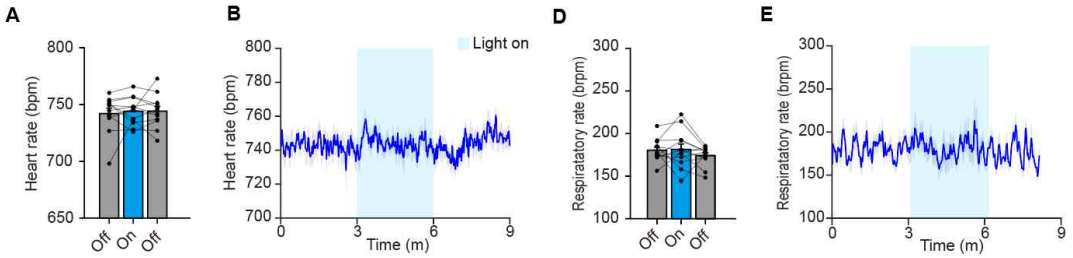

Figure 4. Optogenetic stimulation of LSd^{Sst} neurons did not affect autonomic responses. (A-C) Optogenetic activation of LSd^{Sst} neurons did not affect the heart rate (n = 12, one-way repeated measures ANOVA interaction, F(2,22) = 0.199, p = 0.821). (C-D) Optogenetic activation of LSd^{Sst} neurons did not affect the respiratory rate (n = 12, one-way repeated measures ANOVA interaction, F(2,22) = 1.114, p = 0.339)

5. Activating LSd^{Sst} neurons did not affect stress-related behaviors

To find a behavioral causality of the LSd^{Sst} neurons, I conducted the anxiety-like behavior test during optogenetically activating the LSd^{Sst} neurons. Similar to the loss-of-function experiments (Figure 3), optogenetically activating the LSd^{Sst} neurons also did not affect on time spent in the center zone and frequency to the center (Figures 5 A, B). Velocity, however, was significantly decreased by the activation of the LSd^{Sst} neurons (Figures 5C).

As well as anxiety-like behavior, aggressive behavior is also elicited by stressors (Nelson & Trainor, 2007),while sexual behaviors are disrupted in the stressful circumstances. (Retana-Marquez et al., 1996). In addition, stress causes asocial behaviors such as self-groomingbehaviors (Song et al., 2016). A recent paper has shown that the ventral LS neurons mediate the stress-induced self-grooming (Mu et al., 2020).

Based on these studies, I determined to test the role of the LSd^{Sst} neurons in social behaviors as one of the stress-related behaviorss (Leroy et al., 2018; Wong et al., 2016). However, optogenetic stimulation of LSd^{Sst} neurons neither change the social behaviors nor self-grooming behaviors(Figures 5D-G). Thus, these data suggest that simultaneous activation of the entire LSd^{Sst}

population using optogenetic means, at least under my experimental conditions, has no effect on stress-related behavior or physiology, although alternative interpretations may still exist.

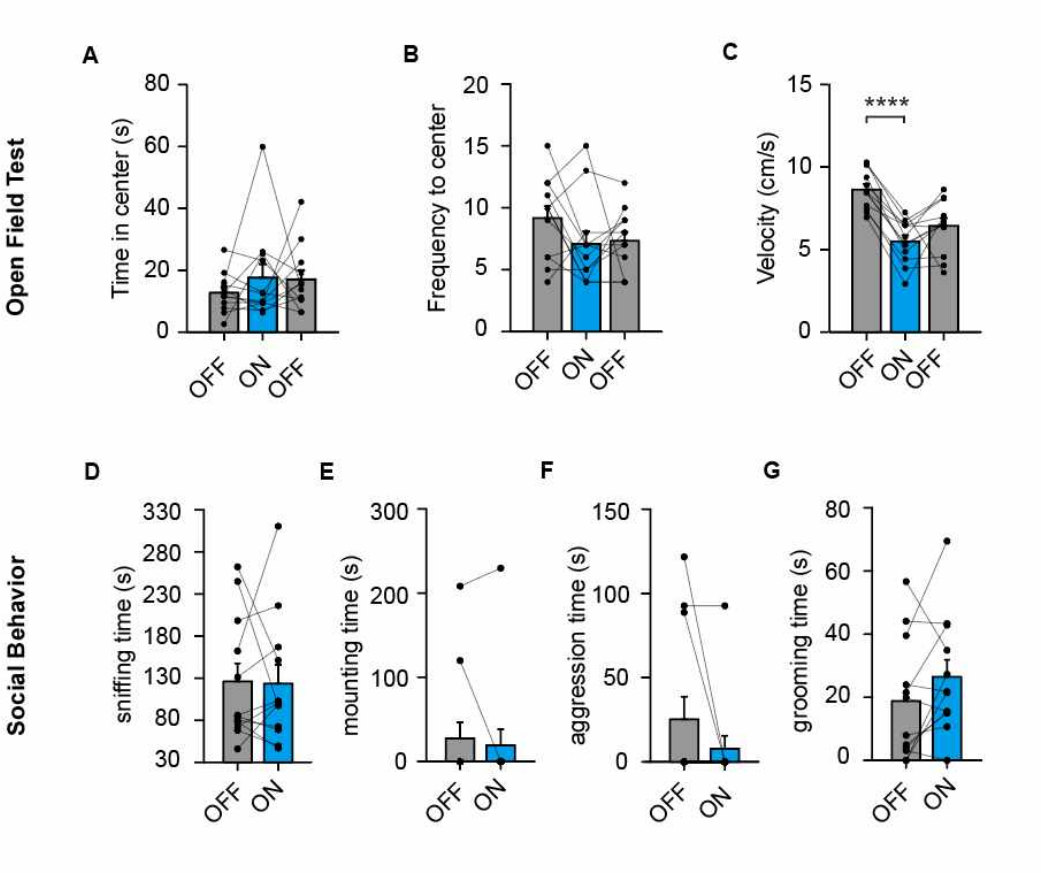

Figure 5. Activating LSd^{Sst} neurons did not affect anxiety-like behavior and social behavior. (A-C) Optogenetic activation of LSd^{Sst} neurons did not affect anxiety-like behavior (n = 12, one-way repeated measures ANOVA interaction, F(2,22) = 0.657, p = 0.529, F(2,22) = 1.87, p = 0.177, F(2,22) = 25.54, p <0.0001) (****p < 0.0001) (D-G) Optogenetic activation of LSd^{Sst} neurons did not affect social behavior (n = 12, p = 0.850, p > 0.999, p = 0.250, p = 0.204)

Discussion

In this study, I investigated the behavioral and autonomic functions of the LSd^{Sst} neurons under the stressful situation. Using fiber photometry, I demonstrated that LSd^{Sst} neurons are activated in response to a stressor (Figure 1). Inhibition of the LSd^{Sst} neurons selectively reduces heart rate (Figure 2). However, the anxiety-like behaviors were unaffected by inhibition of LSd^{Sst} neurons (Figure 3). Optogenetic stimulation of the LSd^{Sst} neurons did not affect autonomic responses (Figure 4). Moreover, activating LSd^{Sst} neurons also did not affect social or anxiety-like behaviors (Figure 5). Taken together, these data suggest that LSd^{Sst} neurons may have a role in regulating the heart rate in stressful circumstances.

My results demonstrate that the inhibition of LSd^{Sst} neurons reduces heart rate in stressful circumstances (Figure 2), but the activation of these neurons is insufficient to alter heart rate (Figure 4). This lack of effect of optogenetic stimulation may be due to thee multiple pathways supporting cardiac responses that work in redundant manners. As such, further systematic investigations will be needed to fully delineate the circuits involved in stress-induced cardiac responses, their specific contributions, and their interactions. In addition, the effect under non-stressful conditions has not yet been examined. To clarify

the autonomic role of LSd^{Sst} neurons, measuring the heart rate changes caused by the modulation of LSd^{Sst} neurons in non-stressful circumstances is necessary.

In this study, I found that the LSd^{Sst} neurons has no effect on anxiety-like, social, and self-grooming behaviors. However, since LS is implicated in other stress-related behaviors such as stress-induced anorexia or depressive behaviors (D. Wang et al., 2021; Xu et al., 2019), I speculate that the LSd^{Sst} neurons may regulate the specific behaviors that I have not examined here. Therefore, additional experiments are still needed to expand understanding of the role of LSd^{Sst} neurons.

The study by Besnard and colleagues also found functional heterogeneity within the LSd^{Sst} neurons population (Besnard et al., 2019), which may lend an explanation to the other reported roles of LSd^{Sst} neurons, such as the modulation of contextual fear discrimination (Besnard et al., 2019) or food-seeking behavior (Carus-Cadavieco et al., 2017). It is possible that different circumstances and tasks activate different subpopulations of LSd^{Sst} neurons. This idea is supported by a recent study that examined the connections of LSd neurons to identify the functionally distinct subpopulations of neurons in this region (Besnard et al., 2020). By optogenetically manipulating the activity, future studies may clarify the function of each pathway.

For the future study, investigating the output regions

would be important to fully understand the role of LS in the autonomic response. According to early data (An et al., 2022), the lateral hypothalamus is one of the projection outputs of LSd^{Sst} neurons. Previous studies show LH neurons mediate restraint-evoked tachycardia (Barretto-de-Souza et al., 2021; Busnardo et al., 2013). I guess LSd^{Sst} neurons could regulate the stress and heart rate via LH neurons.

In addition to the output region study, the locus coeruleus (LC) is a potential input region for relaying stress information in future circuit studies. The LC is a pontine brain area that is a major source of NE to many forebrain areas, including the LS (Chandler et al., 2019; Lindvall & Stenevi, 1978; Moore, 1978; Poe et al., 2020). Noradrenergic neurons in the LC are known to be activated upon diverse stressors (including restraint stress, innate fear, and footshock) (Beas et al., 2018; Chandler et al., 2019; Li et al., 2018; McCall et al., 2015; Poe et al., 2020). Since LSd^{Sst} neurons are directly innervated by LC neurons (An, 2022), it is possible that NE release from LC can modulate the activity of LSd^{Sst} neurons.

Meanwhile, my study presents a step towards this goal by providing a potential entry point to study the circuitry underlying stress-induced cardiac responses. Future investigations in this area will not only shed light on how stress and autonomic responses interact at the circuit and gene level but also provide

clinical insights into the etiology and treatment of stress-induced increased heart rate.

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국문초록

스트레스는 다양한 행동 변화와 자율신경계 반응을 유발하지만, 관여하는 신경 회로 기작은 여전히 불분명하다. 이 논문에서는 소마토스타틴 유전자를 발현하는 외측 중격 뉴런들이 스트레스에 반응하는 것을 보였고, 스트레스 상황에서 외측 중격 소마토스타틴 뉴런의 화학유전학적 억제는 맥박 감소를 일으키는 것을 보였다. 하지만 화학유전학적 억제를 통한 행동적 변화는 관찰되지 않았다. 외측 중격 소마토스타틴 뉴런의 광유전학적 자극은 맥박과 호흡에 영향을 미치지 않고, 불안과 관련된 행동과 사회적 행동 변화에도 영향을 주지 않았다. 이 연구를 통하여 외측 중격 소마토스타틴 뉴런이 스트레스 상황에서 활성화되고 빠른 맥박 활성에 관여한다는 것을 밝혔다.

주요어 : 스트레스, 맥박, 소마토스타틴, 외측 중격

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