ARCHIVAL REPORT

Amygdala-Ventral Pallidum Pathway Decreases Dopamine Activity After Chronic Mild Stress in Rats

Chun-hui Chang and Anthony A. Grace

Background: Major depressive disorder affects more than 15% of the population across their lifespan. In this study, we used the well-characterized unpredictable chronic mild stress (CMS) model of depression to examine this condition.

Methods: Sprague-Dawley rats were presented randomly with mild stressors for 4 weeks, with body weight and sucrose intake monitored weekly. Locomotor activity and elevated plus maze test/forced swim test were conducted on Week 5; ventral tegmental area dopamine (DA) neuron activity was assessed within 1 week after the behavioral test with three indices: DA neuron population activity (defined as the number of spontaneously firing DA neurons); mean firing rate; and percent burst firing (i.e., the proportion of action potentials occurring in bursts).

Results: Consistent with previous studies, we found that, compared with control subjects, rats that underwent the CMS procedure were slower in gaining body weight and developed anxiety- and despair-like behavior. We now report a significant decrease in DA neuron population activity of CMS rats, and this decrease is restored by pharmacologically attenuating the activity of either the basolateral nucleus of the amygdala (BLA) or the ventral pallidum (VP). Moreover, pharmacological activation of the amygdala in nonstressed rats decreases DA neuron population activity similar to that with CMS, which is reversed by blocking the BLA-VP pathway.

Conclusions: The CMS rat depression model is associated with a BLA-VP-ventral tegmental area inhibition of DA neuron activity. This information can provide insight into the circuitry underlying major depressive disorder and serve as a template for refining therapeutic approaches to this disorder.

Key Words: Amygdala, dopamine, rat, unpredictable chronic mild stress, ventral pallidum, ventral tegmental area

Major depressive disorder (MDD) is a complex disorder involving anhedonia, anxiety, and behavioral despair, each of which is associated with alterations in the dopamine (DA) system (1–7). Nonetheless, evidence implicating the DA system in MDD has only recently emerged (8–10). In addition, the basolateral nucleus of the amygdala (BLA) shows increased volume (11–13) and hyper-responsiveness to stress and aversive emotional stimuli (14,15) in MDD. Previously, we demonstrated that acute restraint stress induced a delayed decrease in DA system responsivity that is reversed by pharmacologically attenuating BLA activity (16). Together, these data suggest that the BLA might be involved in a diminished ventral tegmental area (VTA) DA neuron response in MDD.

The unpredictable chronic mild stress (CMS) procedure is a validated animal model of human depression (17). Physical and psychological mild stressors in this procedure induce anxiety-, despair-, and anhedonia-like behaviors in rodents. We used the CMS procedure to study the changes in VTA DA responsivity under depression. We propose that the CMS-induced decrease in VTA DA activity is mediated via the BLA-ventral pallidum (VP)-VTA pathway, given that the BLA projects to the VP (18) and the VP potently inhibits VTA DA neuron population activity (19).

From the Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence to Chun-hui Chang, Department of Neuroscience, University of Pittsburgh, A210 Langley Hall, Pittsburgh, PA 15260; E-mail: changch@pitt.edu.

Received Apr 9, 2013; revised Sep 9, 2013; accepted Sep 18, 2013.

Methods and Materials

Subjects and Materials

Male Sprague-Dawley rats (300–400g; Harlan Laboratories, Hayward, California) were housed for at least 5 days in pairs in a temperature (22°C)- and humidity (47%)-controlled facility upon arrival on a 12-hour light/dark cycle (lights on at 7:00 AM) with food and water available ad libitum. Animals were handled in accordance with the guidelines outlined in the United States Public Health Service *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

Unpredictable CMS Procedure

All rats that underwent the CMS procedure were single-housed. Stressors were randomly presented each week (3–4/week depending on the week) over 4 weeks (20,21) (Figure 1). The stressors included food deprivation, water deprivation followed by 1 hour of empty bottle presentation, overnight illumination, homecage tilting, damp bedding, foreign intruder, strobe light illumination, and presentation of predator odor. Age and body weight (BW)-matched control rats were housed in pairs over the equivalent period of time, except a subgroup that were single-housed to sample individual intake of sucrose solution.

Behavioral Assays

BW and Sucrose Preference Test. Rats acclimated for 5 days were presented with two drinking bottles, one with 1% sucrose solution and one with water (22). Body weight and percentage of 1% sucrose solution intake over 24 hours (9 AM–9 AM the next day) were set as baseline (Day 0), and rats were divided into two matched groups: one subjected to CMS procedure (CMS); and one control (CON). Two drinking bottles were present at all times

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.09.020

© 2014 Society of Biological Psychiatry

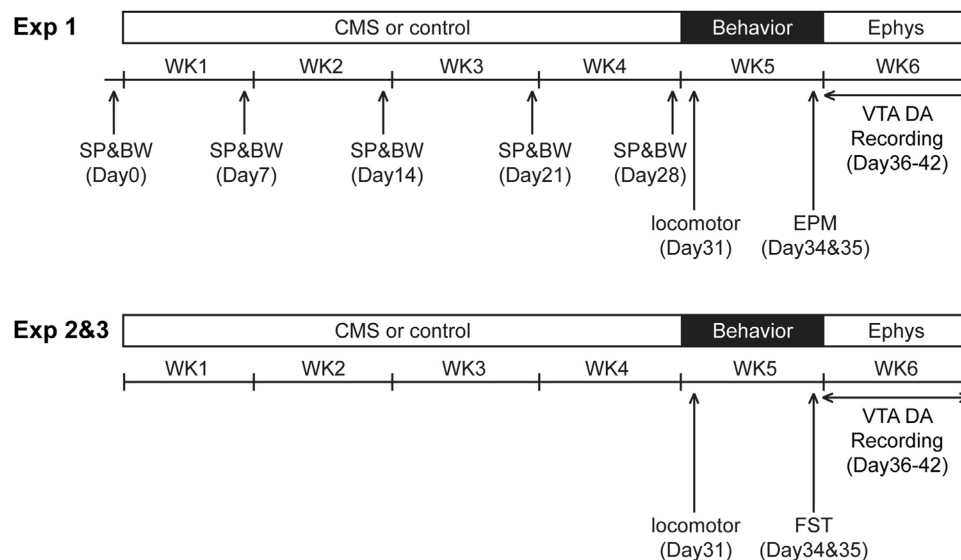

Figure 1. Experimental timeline for rats that underwent the chronic mild stress (CMS) procedure. BW, body weight; EPM, elevated plus maze test; DA, dopamine; Ephys, electrophysiology; Exp, experiment; FST, forced swim test; SP, sucrose preference test; VTA, ventral tegmental area; WK, week.

with the position alternated daily. At the end of each week (Days 7, 14, 21, 28), the percentage of 1% sucrose solution intake over 24 hours was sampled, and body weight was measured.

Locomotor Activity. General locomotor activity indexed as the total distance traveled (centimeters) was measured (Day 31; 9 AM–12 PM) by placing the rat into an open-field arena (Coulbourn Instruments, Whitehall, Pennsylvania). Spontaneous activity was monitored for 10 min by beam breaks with TruScan software (Coulbourn Instruments).

Elevated Plus Maze. One day before the test (Day 34), all rats were handled and acclimated for 2 hours (12 PM–2 PM) to the elevated plus maze (Med Associates, St. Albans, Vermont) room. On the test day (Day 35; 9 AM–12 PM), each rat was placed onto the maze facing one of the closed arms. Over 5 min, the total time spent in the open arms as the percentage of total time spent in the open plus closed arms and the open arm entries as the percentage of total entries in open plus closed arms were measured (23).

Forced Swim Test. The forced swim test (FST) took place in a cylinder (50 cm in height × 20 cm in diameter) filled with water (23°C–25°C) to 30 cm. One day before the test (Day 34; 9 AM–5 PM), a pre-exposure of 15 min swimming was given to ensure that the rats quickly adopt an immobile posture on the test day. On the test day (Day 35; 9 AM–5 PM), each rat was placed in the cylinder for 5 min, and the total time spent immobile was measured (24).

Electrophysiological Recordings

Single-unit extracellular recordings were performed on rats (9 AM–6 PM) anesthetized with 8% chloral hydrate (400 mg/kg IP), and VTA recordings (from bregma: anterior-posterior [AP] −5.3 to −5.7 mm; medial-lateral [ML] −.6 to −1.0 mm; ventral from brain surface: −6.5 to −9.0 mm) were made as previously described (16). The DA neurons were identified with open filter setting (50–16 kHz bandpass) and distinguished by their unique long-duration waveform (>2.5 msec), slow irregular firing rate, and other well-established criteria (25,26), which enabled accurate identification of the large majority of DA neurons recorded (27). Three parameters of VTA DA neuron activity were calculated: 1) "population activity," or the relative number of spontaneously firing DA neurons, was assessed by passing the electrode through the VTA in a predetermined grid pattern of 9 tracks separated by 200 μm; all spontaneously active DA neurons encountered/electrode track were counted (Figure 2A,B); 2) for each DA neuron, 3 min of activity was recorded to determine the "firing rate"; and 3) for each DA neuron, 3 min of activity was recorded to determine the "percentage burst firing" (Figure 2C).

For Experiments (Exp) 1–3 (CMS), the recordings were done on Days 36–42, with the recording order counterbalanced among groups. For Exp 4 and 5, recordings were conducted on non-stressed, naïve rats.

Drug Administration

For local drug administration, a 28-gauge stainless-steel cannula (Plastics One, Roanoke, Virginia) was lowered into the BLA (relative to bregma: AP −2.9 mm; ML +5.0 mm; dorsal-ventral [DV] −8.6 mm) or the VP (relative to bregma: AP −.3 mm; ML +2.0 mm; DV −7.8 mm). All drugs were freshly mixed in Dulbecco's phosphate-buffered saline buffer (VEH) (Sigma, St. Louis, Missouri), with the doses chosen on the basis of previously published reports. Depending on the design of each experiment, .2 μL of tetrodotoxin (TTX) (1 μmol/L) (Sigma) (28), *N*-methyl-D-aspartic acid (NMDA) (.75 μg) (Sigma) (28), or VEH was infused into the BLA, whereas .5 μL of kynurenic acid (KYN) (5 μg) (Sigma) (28) or VEH was infused into the VP. Drugs were delivered at .2 μL/min, and another 1 min was allowed for diffusion. The cannula was then removed, immediately followed by single unit recordings of VTA DA neurons.

Data Analysis and Statistics

Single-unit neuron activity was analyzed with Powerlab (ADInstruments, Colorado Springs, Colorado) and Nex (NEX Technologies, NexTech Systems, Tampa, Florida) software. All data are represented as the mean ± SEM and were submitted to analysis of variance (ANOVA) or *t* test. Post hoc comparisons with Fisher's least significant difference test was performed for ANOVAs that achieved a significance of $p < .05$. All statistics were calculated with SPSS (IBM, Armonk, New York) or SigmaStat (Systat Software, Chicago, Illinois).

Download English Version:

https://daneshyari.com/en/article/6227313

Download Persian Version:

https://daneshyari.com/article/6227313

Daneshyari.com