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The participation of a neurocircuit from the paraventricular thalamus to amygdala in the depressive like behavior

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ABSTRACT

Depression is a neuropsychological disease derived from genetic, biochemical, environmental, and psychological factors. However the neurocircuits involved in it are not clear. We introduced the forced swimming test (FST) as a model of the depressive like behavior. In our study, the participation of projections from paraventricular nucleus of the thalamus (PVT) in FST was detected. The retrograde tracing combined with immunofluorescent detection of c-fos was used. Our results showed that the FST greatly increased the c-fos level in PVT and the central amygdale (CE) neurons. These populations of activated neurons in the PVT and the CE were also labeled by the retrograde tracer FG injected in the CE, suggesting that the activation of PVT was involved in this depressive like behavior by relaying information to the CE.

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Depression is a mental disorder characterized as low or depressed mood, anhedonia and low energy or fatigue [29]. Other symptoms are also present in patients, such as sleep and psychomotor disturbances, pessimism, guilty feelings, low self-esteem, suicidal tendencies, and food-intake and body-weight dys-regulation. Depression is the most prevalent affective disorders in human beings worldwide with estimates of lifetime prevalence as high as 21% of the general population in some developed countries.

Research indicates that depressive illnesses are disorders of the brain involving several neurotransmitters and nuclei. One hypothesis is dys-regulation by the hippocampus and amygdala of the hypothalamic-pituitary-adrenal axis. During a pathologically stressful process, the hippocampus exerts an inhibitory influence on hypothalamic CRF-containing neurons via a polysynaptic circuit, while the amygdala exerts a direct excitatory influence on the same neurons [21]. In the model of depression, the resulting hypercortisolemia can pathologically reduce the birth of new granule cell neurons in the adult hippocampal dentate gyrus [6], which contributes to the brain imaging findings and to the symptomatology of stress in humans.

Several classes of antidepressant treatment increase the number of BrdU-labeled cells in the dentate gyrus and hilus of the hippocampus of rats [14]. Other research also shows that the cellular molecular changes occur in the brain reward pathway of nucleus accumbens-ventral tegmental area with increased CREB activity following forced swimming [18]. Many recent studies focus on the integration of neurocircuits including amygdala, striatum, hypothalamus, hippocampus and neocortex to formulate a more complete neurocircuitry of mood and emotional disease, such as depression. However the exact changes in neurocircuitry during the disease are not clear, especially in the beginning process of depressive like behavior.

In our research, the specific projections to the central amygdala were studied by the retrograde tracer fluoro-gold (FG) labeling in the rats followed by the forced swimming test (FST) to induce a depressive like behavior. Our results showed that the c-fos positive neurons in the circuit from the paraventricular thalamic nucleus (PVT) to the central amygdala (CE) greatly increased after the forced swimming, indicating that the activation of PVT-CE circuit will participate in the process induced by the acute stressful event through information transferring.

Male Sprague Dawley rats (Shanghai Center of Experimental Animal, Chinese Academy of Sciences) weighing 250–280 g were housed and maintained on a 12:12 h reversed day/light cycle with free access to food and water. All experiments were conducted in strict accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. Eighteen rats in total were used in this study, including 4 rats for neurocircuits identification, 14 rats for behavior test and immunochemistry test. Then there are 7 rats in control group and 7 rats in FST group.

FG (Fluorochrome Inc., Denver CO) is used extensively as a retrograde axonal tracer to determine neuroanatomical connectivity. Then FG was introduced in our study by the microinjection into

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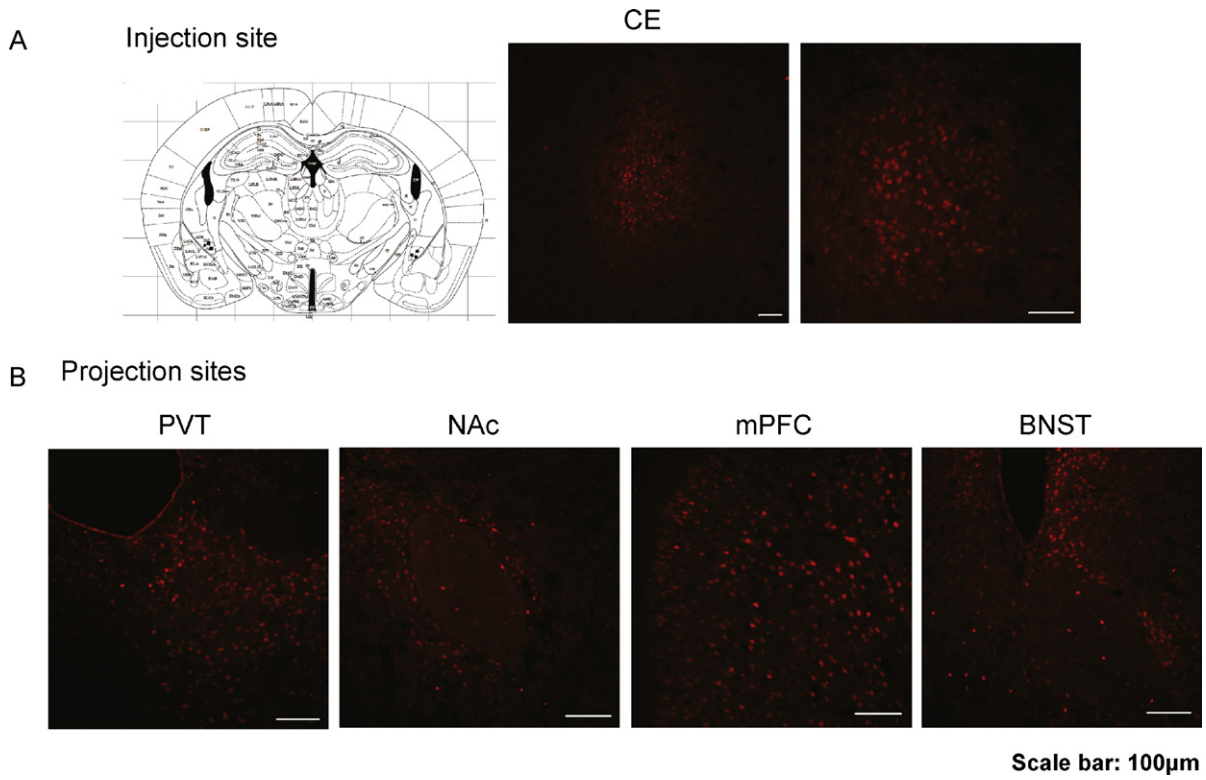

Fig. 1. The brain nuclei send the projection to CE. (A) The black dots in the graph represent the location where the FG was injected (left). FG labeled neurons in CE under 10× len (middle) and 20× len (right). (B) The neurons labeled with FG in PVT under 20× len. (C) The neurons labeled with FG in NAc under 20× len. (D) The neurons labeled with FG in mPFC under 20× len. (E) The neurons labeled with FG in BNST under 20× len.

central amygdala (CE) of SD rats. FG was dissolved in 2% (w/v) double distilled water. It is taken up by the intact axon terminals and the injured axons but not by the intact axons with nonterminal sites [23]. Intact axonal uptake occurs via endocytosis at nerve terminals [25]. After retrograde transport, FG labels neuronal soma and dendrites. In the soma, FG is associated with vesicles in the cytoplasm, the plasma membrane, and the nucleus. It does not diffuse from labeled neurons, and it is not transported trans-synaptically. In this study FG was chosen for the retrograde research of the neuronal projection to amygdala.

For surgery and microinjection, chloral hydrate-anaesthetized rats were positioned in a stereotaxic apparatus (NARISHIGE Scientific Instrument LAB). A small hole was drilled in the skull to allow insertion of a micro syringe. Microinjections into the CE were made by the digitally controlled pressure injector (Stoelting) with the parameters (AP: −2.0 mm, ML: ±4.0 mm, DV: −7.5 mm). Hamilton syringe (Hamilton, Reno, NV) was used for the injection. Animals received bilateral microinjections of 0.1 ul FG at a rate of 0.02 μl/min for 5 min by the nanopump (Stoelting, QSI). Under this volume no obvious lesions were found in CE and other area labeled with FG. Following the microinjections, the stainless steel micro injector was left in place for 10 min and withdrawn in 10 min in order to prevent the solution from diffusing away from the tips. After recovery of one week, the rats were perfused with saline and fixed with 4% paraformaldehyde in 0.1 M phosphate buffer (pH = 7.4). The brain was frozen and cut into 30 μm thick transverse sections with a sliding microtome (Leica, Germany). The slices were scanned and analyzed under confocal laser microscope scanner (Carl Zeiss, Oberkochen, Germany). FG can be visualized directly by fluorescence microscopy using an ultraviolet filter (excitation, 365 nm; emission, 420 nm) [12,24]. The positive neurons are identified with the orange particles in the cell under confocal scanning. We use red color as the pseudo color for the FG positive cells.

After one week recovery from the surgery, the FST was performed in SD rats with a glass cylinder (40 cm in diameter and 60 cm in depth) of 24 ± 1 °C water filled to a depth of 40 cm. Twenty-four hours after adaptation to the cylinder without water, rats were placed in water for 5 min. Activity during the swimming test was video-recorded for subsequent behavioral analysis. In the FST group, the specific behavioral components of active behavior were investigated by counting the predominant behavior events over a 5-s interval. Firstly, the climbing behavior is defined as upward-directed movements of the forepaws along the side of the swim chamber. Secondly, the swimming behavior is defined as the horizontal movement throughout the swim chamber that also includes crossing into another quadrant. Thirdly and most importantly, the immobility is defined as when no additional activity is observed other than that required to keep the rat's head above the water. Immobility can be detected as lack of movement of lack of movement of at least three paws [28]. Struggling was defined as vigorous movement of all four paws, with the rat in a relatively upright position [9].

Rats injected with FG one week ago were anaesthetized with overdose of chloral hydrate 2 h after the forced swimming test. After disappearance of withdrawal reflexes and cessation of breathing, a needle was inserted through the left ventricle into the aorta. The right atrium was opened and the vascular system was perfused briefly with about 350 ml saline (pH = 7.4) followed by approximately 350 ml of 4% paraformaldehyde in 0.1 M phosphate buffer (pH = 7.4). Then the brains were removed quickly and placed within sucrose in gradient from 10% to 30%. Brain slices including PVT and CE (30 μm) were incubated overnight at 4 °C with primary antibody c-fos (1:1000, Ab5, Oncogene Science), then they were incubated for 1 h at room temperature with biotinylated goat anti-rabbit antibody (1:200, Vector Laboratories) and processed with avidin-biotinylated horseradish peroxidase complex (1:500, Elite ABC kit, Vector Laboratories) for 1 h at room temperature. The

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