Progress in Neuro-Psychopharmacology & Biological Psychiatry 60 (2015) 26–35

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Decision-making deficits associated with disrupted synchronization between basolateral amygdala and anterior cingulate cortex in rats after tooth loss

Xiaoxiang Xu [1], Bing Cao [1], Jun Wang, Tianran Yu, Ying Li *

Department of Biomedical Science, City University of Hong Kong, Hong Kong, China
Centre for Biosystems, Neuroscience, and Nanotechnology, City University of Hong Kong, Hong Kong, China

ARTICLE INFO

Article history:
Received 30 January 2015
Accepted 5 February 2015
Available online 12 February 2015

Keywords:
Amygdala
Anterior cingulate cortex
Decision-making
Theta oscillation
Tooth loss

ABSTRACT

Human studies have shown that multiple teeth loss was significantly associated with cognitive impairment, dementia and Alzheimer's disease. However, the causal relationship between tooth loss and cognitive deficits has not been clarified. Rodents demonstrate human-like cognitive faculties. In this study by performing rat gambling task (RGT), we reported that prolonged tooth loss condition by extracting all left molars in the rats led to an increase in the proportion of poor decision-makers, and decrease in the proportion of good decision-makers compared with controls. No influence was detected on the general activity and motivation after tooth loss. Recent experiments have shown that decision-making performances in the RGT rely on the functional integrity of the amygdala and anterior cingulate cortex (ACC). The theta band brain oscillation has been acknowledged for extensive cognitive functions. Here, we performed multiple-electrode array recordings of local field potential (LFP) in anesthetized rats. The results exhibited an increase in accumulative power of the theta frequency of LFP in the basolateral amygdala (BLA) and decrease of theta power in the ACC in tooth loss rats. Furthermore, cross-correlation analysis displayed that tooth loss suppressed the synchronization of theta frequency of LFP between the BLA and ACC, indicating reduced neuronal communications between these two regions. In conclusion, we demonstrate for the first time that tooth loss leads to higher-order cognitive deficits accompanied by the alteration of theta frequency of LFP in brain circuitries and disruption of neural network integrity.

1. Introduction

Extensive evidence has suggested that multiple teeth loss is significantly associated with cognitive impairment. Population studies in northern Sweden (Bergdahl et al., 2007), Japan (Saito et al., 2013), Finland (Syrjälä et al., 2007) and Germany (Grabe et al., 2009) found lower Mini-Mental State Examination (MMSE) scores in multiple teeth loss or edentulous people. A cross-sectional survey in Korea reported that fewer teeth was significantly related to the risk of dementia and Alzheimer's disease in people aged 65 and older (Kim et al., 2007). However, the findings of previous reports also suggested that other potential confounders such as age, education levels, nutritional status, socioeconomic status, and masticatory function may account for the association between tooth loss and cognitive deficits (Kim et al., 2007; Lexomboon et al., 2012). Therefore, a direct causal relationship between tooth loss and impaired cognitive function in healthy population has not been clarified.

Cognition refers to a set of mental processes, including attention, memory, evaluation, decision-making, etc. Cognitive ability declines when aging (Drag and Bieliauskas, 2010). Low cognitive ability, even in the normal range, predicts poor health outcomes (John et al., 2002; Pavlik et al., 2003). Making a decision under complicated and uncertain conditions is a basic cognitive process for adaption relying on the integration of several executive functions. Impaired decision-making has been demonstrated to represent a key symptom in many mental disorders (Paulus, 2007; Rahman et al., 2001). Various neuropsychological tests to evaluate cognitive ability have been used in research of cognition. In humans, decision-making has been accurately modeled using the Iowa gambling task (IGT) in the laboratory (Bechara et al., 1997, 1999, 2002). In behavioral tasks for animals, several psychiatric symptoms addressing higher-order cognitive dysfunctions have been reproduced (Nestler, 2006). Of note, no animal studies to date have examined the decision-making deficits after multiple teeth loss. In this study we used an animal model of

Abbreviations: RGT, Rat gambling task; ACC, Anterior cingulate cortex; LFP, Local field potential; BLA, Basolateral amygdala; MMSE, Mini-Mental State Examination; IGT, Lowa gambling task; PFC, Prefrontal cortex; LED, Light-emitting diode; PSD, Power spectral densities; ANOVA, one-way or two-way analysis of variance; Cg1, Cingulate cortex, area 1; Cg2, Cingulate cortex, area 2

* Corresponding author at: Department of Biomedical Science, Centre for Biosystems, Neuroscience, and Nanotechnology, City University of Hong Kong, Tat Chee Avenue, Kowloon, Hong Kong, China. Tel.: +852 3442 2669; fax: +852 3442 0522.
E-mail address: yingli@cityu.edu.hk (Y. Li).

[1] Authors Xiaoxiang Xu and Bing Cao contributed equally to this work.

http://dx.doi.org/10.1016/j.pnpbp.2015.02.002
0278-5846/

decision-making test, the rat gambling task (RGT) (Rivalan et al., 2009), to evaluate cognitive function in rats after tooth loss. Similar to the findings of most advantageous strategy from the IGT utilized in human studies, most normal rats can learn to maximize their food reward by reasoning and preferring more profitable options associated with smaller immediate gain but lower risk of punishment (time-out) during RGT.

Recent experiments have exhibited that decision-making performances in the RGT depend on the integrated function of several subregions of the prefrontal cortex (PFC), especially the prelimbic, cingulated and orbitofrontal cortices (Rivalan et al., 2011; Zeeb and Winstanley, 2011). There are evidences suggesting that the anterior cingulated cortex (ACC) serves conflict control in the information stream and memory processing in the visual pain (Cao et al., 2008; Fan et al., 2009) and the prolonged negative affection (Botvinick et al., 2004; Yan et al., 2012). Recently, we characterized the facilitation of synaptic transmission in the medial thalamus–ACC pathway in viscerally hypersensitive rats (Wang et al., 2013), indicating the enhancement of visceral pain responses parallels with long-term neuroplasticity in the ACC, where nociceptive information may be stored. Moreover, several subcortical structures have been demonstrated to be involved in differentially mediating decision-making process, including basolateral nucleus of amygdala (BLA) (Floresco et al., 2008). The reciprocal connections between the BLA and medial PFC including the ACC have been clearly exhibited previously (Bacon et al., 1996; Cassell and Wright, 1986). Indeed, an interconnected neural circuitry between the BLA and the ACC region of the medial PFC guides behaviors in certain types of cost–benefit decision-making task (Floresco and Ghods-Sharifi, 2007). The theta band brain oscillation has been accepted for extensive cognitive functions (Başar et al., 2001; Jensen and Tesche, 2002; Klimesch, 1999). Recent neurobiological studies of memory and perception in human share common observations of coherency of the theta oscillations and action potential activity. Theta band activity of local field potential (LFP) is mainly observed in the limbic system including the hippocampus and the cingulated cortex as well as in the PFC (Ishii et al., 1999; Miller, 1991; Raghavachari et al., 2006). However, until now the alteration of theta oscillations within and between the amygdala–ACC circuitry under oral pathological conditions has not been explored. Therefore, we sought to characterize if tooth loss disrupts the amygdala–ACC network integrity, which is associated with decision-making deficits.

In the current study, the decision-making of rats was tested by RGT eight weeks after left molar extraction. Then, the rats were anesthetized and multiple-electrode array recordings of LFP were performed. Power spectral density analysis showed an increase in accumulative power of the theta band of LFP in the BLA in tooth loss rats. In contrast, reduction of theta power was found in the ACC. Finally, cross-correlation analysis revealed that tooth loss led to suppressed synchronization of theta oscillation between the BLA and ACC, indicating reduced neuronal communications between these two regions.

2. Materials

2.1. Animals

A total of sixty male Sprague–Dawley rats (3 month old, 420–450 g, Laboratory Animal Service Centre of the Chinese University of Hong Kong, China) were used. They were settled in a temperature controlled room (25 °C) under a 12 h light/dark cycle with food and water ad libitum except for the period of RGT when food was moderately restricted for each rat (90% of free feeding weight). The protocols we used were reviewed and approved by the Committee on the Use and Care of Animals at the City University of Hong Kong and the licensing authority for conduction experiments of the Department of Health of Hong Kong (No. (14–81) in DH/HA&P/8/2/5 Pt. 3).

2.2. Tooth extraction

Rats were randomly assigned into tooth loss group and control group ($n = 30$ in each). In tooth loss group, rat was anesthetized with isoflurane (5% induction, 2% maintenance). All left upper and lower molars were extracted carefully with hemostatic forceps following gingiva dissection with a sharp dental probe. Sterile gauze was applied to suppress bleeding. In control group, similar procedures including anesthetization and gingiva dissection were performed, but no tooth was extracted. One week after the operation, all rats were anesthetized in the same way and the wound was examined to evaluate the healing status and ensure no debris was left. Body weight was monitored before and after tooth extraction weekly. Food intake was monitored before and after tooth extraction daily until it resumed to the original level.

2.3. Behavioral assessments

Eight weeks after molar extraction, open field test and rat gambling task (RGT) were performed to evaluate the locomotor activity and decision-making behavior of rats. Rats were habituated in the testing room and handled for 3 days before tests started. The time of tests began at 9:00 am and ended before 1:00 pm (early phase of the light cycle) each day.

2.4. Open field test

A black square box ($80 \times 80 \times 40$ cm) was used to evaluate the locomotor activity of rats. Rats were gently placed in one corner of this novel arena and free to explore the field for 5 min under dim light. The test process was recorded via a video camera on the ceiling above. Time of freezing and grooming (s), total traveled distance (m), and times of rearing were measured by ANY-maze system (Stoelting Co., Wood Dale, IL, USA). Defecation pieces were also counted after each test.

2.5. Rat gambling task

The rat gambling task (RGT) has been developed to test the decision-making capacities in rats via a conflict between immediate and long-term gratification (food reward) (de Visser et al., 2011). The procedure we adopted was a single session paradigm of RGT.

The operant chambers ($28 \times 30 \times 34$ cm) for RGT (Imetronic, Pessac, France) consisted of four apertures on the front curved wall each of which was illuminated dimly with a white light-emitting diode (LED) inside and one food tray on the opposite wall connected to a dispenser outside the chamber for releasing food pellets as reward (45 mg, TestDiet, USA). Infra-red detector was equipped in each aperture and the food tray. A transparent central opening partition (7 cm × 7 cm) divided the chamber into two parts at the middle, which permitted equal distance to each aperture from the opening. To complete this food-driven task, daily food was moderately restricted for each rat to maintain its weight to 90% of free feeding weight.

During the training stage, rat was placed in the chamber for 40 min each day. Rat gradually learned the association between the nose-poke action into the illuminated aperture and the release of food pellet in the food tray. When an aperture was selected, LEDs of the other three were inactivated until the reward was collected. Two consecutive nose-pokes in the same aperture were necessary to trigger pellet release, to make sure rats made the choice intentionally. Each rat must obtain 100 pellets within 30 min at the end of training. Then, two 5-min sessions were conducted. The first was set as two pellets released after a choice was made and the second set as one pellet, to habituate rats for the variation of pellet number during the test. The training phase usually lasted 7 to 10 days.

The 60-min test was performed the following day. Rat was free to make choices among the four apertures (A–D) as it was in training phase, however, different choices were associated with different