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INCREASED DEPRESSION-LIKE BEHAVIORS WITH DYSFUNCTIONS IN THE STRESS AXIS AND THE REWARD CENTER BY FREE ACCESS TO HIGHLY PALATABLE FOOD

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Abstract—This study was conducted to examine the behavioral consequences of unlimited consumption of highly palatable food (HPF) and investigate its underlying neural mechanisms. Male Sprague–Dawley rats had free access to chocolate cookie rich in fat (HPF) in addition to *ad libitum* chow and the control group received chow only. Rats were subjected to behavioral tests during the 2nd week of food condition; i.e. ambulatory activity test on the 8th, elevated plus maze test (EPM) on the 10th and forced swim test (FST) on the 14th day of food condition. After 8 days of food condition, another group of rats were placed in a restraint box and tail bloods were collected at 0, 20, 60, and 120 time points during 2 h of restraint period, used for the plasma corticosterone assay. At the end of restraint session, rats were sacrificed and the tissue sections of the nucleus accumbens (NAc) were processed for c-Fos immunohistochemistry. Ambulatory activities and the scores of EPM were not significantly affected by unlimited cookie consumption. However, immobility duration during FST was increased, and swim decreased, in the rats received free cookie access compared with control rats. Stress-induced corticosterone increase was exaggerated in cookie-fed rats, while the stress-induced c-Fos expression in the NAc was blunted, compared to control rats. Results suggest that free access to HPF may lead to the development of depression-like behaviors in rats, likely in relation with dysfunctions in the hypothalamic–pituitary–adrenal axis and the reward center.

Key words: corticosterone, food intake, nucleus accumbens, stress.

INTRODUCTION

Palatability of food plays an important role in the regulation of ingestion (Saper et al., 2002). It is known that animals prefer sweet and fatty edibles and often consume more than is needed for homeostatic repletion. The nucleus accumbens (NAc) is known to be involved in palatability-induced feeding behavior. The brain reward system comprising the NAc is the neural substrate for the intracranial self-stimulation phenomenon and the rewarding effects of addictive drugs and the same neural circuitries are concerned with the taste reward system (Yamamoto, 2008). The taste reactivity test of hedonic palatability has shown that morphine microinjection into the NAc shell not only facilitates feeding but also selectively increases positive hedonic patterns of behavioral affective reaction elicited by oral sucrose (Pecina and Berridge, 2000). Sucrose sham-feeding proportionally increased dopamine levels in the NAc depending on the concentration of sucrose (Hajnal et al., 2004), suggesting that the meso-limbic dopamine system is implicated in a reward effect of taste palatability.

The NAc is activated responding to behavioral stress paradigm (Imperato et al., 1992; Saal et al., 2003; Jahng et al., 2010), suggesting its implication in the stress-responsive regulation of the hypothalamic–pituitary–adrenal (HPA) axis. Gastric infusion of glucose significantly increases c-Fos expression, a conventional marker for neuronal activation, not only in the NAc but also in the hypothalamic paraventricular nucleus which is located in the center of the HPA axis activation (Otsubo et al., 2011). This idea of hypothalamic–NAc regulation was further supported by a report demonstrating that glucocorticoid antagonist RU486 inhibits stress-induced synaptic activation in the NAc (Saal et al., 2003). Also, it was reported that stressors stimulate the secretion of dopamine over the NAc in proportion to cortisol responses (Oswald et al., 2005; Wand et al., 2007), and treatment with glucocorticoids increases meso-limbic dopamine levels (Oswald et al., 2005).

Studies have suggested that the HPA axis dysfunction is implicated in the pathophysiology of anxiety (Albenidou-Farmaki et al., 2008) and depression (Heim et al., 2000). Our previous studies have suggested that the HPA axis dysfunction and a blunted neuronal activation and dopamine release in the NAc responding to acute stress are associated with disordered psycho-emotional behaviors in rats experienced early life stress (Lee et al., 2007; Noh et al., 2008; Jahng et al., 2010). In human, experimentally induced negative mood is improved immediately and selectively after eating

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Abbreviations: AA, ambulatory activity test; ANOVA, analysis of variance; EPM, elevated plus maze test; FST, forced swim test; HPA, hypothalamic–pituitary–adrenal; HPF, highly palatable food; NAc, nucleus accumbens.

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palatable food, and this effect is most pronounced in persons scoring high on emotional eating (Macht and Muller, 2007). This suggests that immediate positive affective reactions elicited by palatable foods diminish the impact of stress. Indeed, in rats with early life stress experience, palatable food access during adolescence and youth normalized the HPA axis dysfunction and improved their psycho-emotional symptoms (Lee et al., in press).

Despite of the putative-positive effects of high fat and carbohydrate ''comfort foods'' (Wansink et al., 2003) improving the negative mood of stressed subjects, studies have suggested that consumption of palatable food containing chocolate may affect functions of the HPA axis and/or the reward system and result in psycho-emotional disturbances in normal subjects. Chocolate has been viewed to interact with neurotransmitters such as dopamine, serotonin and endorphins (Parker et al., 2006), which contribute to appetite, reward and regulation of mood (Wurtman and Wurtman, 1995; Bruinsma and Taren, 1999). Recently, it was reported that long-term free access to chocolate bar in addition to *ad libitum* chow increases oxidative stress and DNA breaks in the hippocampus and the striatum of rats (Krolow et al., 2010). The hippocampus is known to be involved in the feedback regulation of the HPA axis activity, and dysfunctions in the hippocampus and the ventral striatum are associated with symptoms of depression (MacQueen et al., 2003; Sahay and Hen, 2007; Gorwood, 2008; Jahng, 2011). Also, free access to high-fat diet increased both basal and stress-induced secretion of adrenocorticotrophic hormone and corticosterone in naïve rats (Tannenbaum et al., 1997; Kamara et al., 1998), suggesting that chronic dietary fat is itself a stressor, possibly resulting in psycho-emotional disturbances. In this study, anxiety- and depression-like behaviors were examined in rats with free access to chocolate cookie rich in fat, in parallel with stress-responsive increase of corticosterone and c-Fos expression in the NAc.

EXPERIMENTAL PROCEDURES

Animals

Male Sprague–Dawley rats (200–250 g, Samtako Bio, Osan, Korea) were individually housed and maintained in a specific pathogen-free (SPF) barrier zone with the constantly-controlled temperature (22 ± 1 °C) and humidity (55%) on a 12-h light–dark cycle (lights-on at 0700 h) in the Seoul National University Animal Facility Breeding Colony. Standard laboratory food (Purina Rodent Chow, Purina Co., Seoul, Korea) and membrane-filtered purified water were available *ad libitum*. Animals were cared according to the Guideline for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH Guidelines for the Care and Use of Laboratory Animals, revised 1996. All animal protocols were approved by the Committee for the Care and Use of Laboratory Animals at the Seoul National University.

Food condition

Rats in the chow + HPF (highly palatable food) group received free access to chocolate cookie (Oreo cookie, Kraft Foods Global, Inc., East Hanover, NJ, USA) additionally to *ad libitum* chow access, and the control rats (chow) received chow only. During the experimental period, previously weighed amounts of standard lab chow and chocolate cookie were offered, and the remaining amount was measured each day to evaluate the consumption. Food condition was continued throughout the whole experimental period.

Ambulatory activity

Rats in each food condition (6 chow + HPF and 6 chow rats) were subjected to the ambulatory activity test (AA) after 8 days of HPF access. On each trial, the rat was placed in the center of the activity chamber (43.2 cm in length, 42.2 cm in width, and 30.5 cm in height, MED Associates, St. Albans, VT, USA), a transparent acryl chamber equipped with two horizontal planes of 16 infrared photocell-detector pairs placed in x, y dimension, spaced 2.5 cm apart, and its ambulatory activity was monitored by the computerized system for 30 min. Light condition of the test room was maintained in the same intensity with animal rooms under day-light condition. Ambulatory activity was measured as the total counts of beam interruptions in the horizontal sensor during each consecutive 5-min session. The activity chamber was cleaned with 70% ethanol after each use to eliminate any olfactory cues of the previously tested rat.

Elevated plus maze

Two days after the AA (after 10 days of HPF access), rats were subjected to the behavioral assessment in an elevated plus maze, a plus-shaped acryl maze with two opposite open arms (50 cm in length and 10 cm in width) and two opposite closed arms (50 cm in length, 10 cm in width, and 31 cm in height), extending out from a central platform (10 cm × 10 cm). The whole apparatus was elevated 50 cm above the floor. The test procedure was followed as previously described (Daniels et al., 2004). Each rat was placed in the center of the maze facing one of the open arms, and then allowed to explore the open or closed arms of the maze for 5 min. The time spent in the different arms was recorded, respectively. Four paws had to be inside the entrance line to each arm, which signaled the start of the time spent in the specific arm, and then the end time was recorded when all four paws were outside the line again. The maze was cleaned with 70% ethanol after each test to prevent influences of the previously tested rat.

Forced swim test (FST)

Four days after the elevated plus maze test (EPM) (after 14 days of HPF access), rats were subjected to the FST according to the method previously described (Porsolt et al., 1977). Each rat was allowed to swim in a glass cylinder (54 cm in height and 24 cm in diameter) filled