

**研 究 者 : Serirukchutarungsee Saranya**

(所属 : Department of Orthodontic Science, Tokyo Medical and Dental University)

**研究題目 : TWO-GENERATION EXPOSURE TO A HIGH-FAT DIET INDUCES THE CHANGE OF SALTY TASTE PREFERENCE IN RATS**

**目 的 :**

This study aimed to investigate the combined effect of maternal HFD consumption during pregnancy and lactation, as well as HFD intake in the early life of rat offspring, on the peripheral taste system.

**対象および方法 :**

Eleven-week-old female pregnant Wistar rats were divided into the standard diet (SD) and high-fat diet (HD) groups. The SD group (n=5) was fed a standard diet, and the HD group (n=5) was fed a high-fat diet from 7 days of pregnancy until the end of the lactation period. During the lactation period, each mother rat in the SD and HD groups was caged with their pups. After weaning, all rats in the SD and HD groups were euthanized at 17 weeks of age. Male and female offspring from the SD and HD mother rats were randomly selected. Offspring from the SD and HD groups were randomly divided into two group sets : three-week-old and ten-week-old. The three-week-old group set consisted of nine male and nine female offspring from the SD and HD groups named SDM3w (n=9), SDF3w (n=9), HDM3w (n=9), and HDF3w (n=9), respectively. Body weight and fasting blood sugar levels were measured before euthanasia at 3 weeks of age. In addition, the ten-week-old group set consisted of six male and six female offspring from the SD and HD groups assigned to the following groups : SDM10w (n=6), SDF10w (n=6), HDM10w (n=6), and HDF10w (n=6). The offspring in this group set were weaned on the same diet as their mothers and raised individually in a cage. Daily food intake, energy intake, weekly body weight, and blood glucose level were measured. The taste preference behaviors were studied using the two-bottle taste preference test analyzed five basic tastes (sweet, bitter, umami, sour, and salty) from 3 weeks of age until the day of euthanasia at 10 weeks of age.

**結果および考察 :**

The weaning body weights of the HDM3w and HDF3w groups were significantly higher than those of the SDM3w and SDF3w groups, respectively. In the SDM10w, SDF10w, HDM10w, and HDF10w groups, the weekly body weight was significantly higher in the HDM10w group than in the SDM10w group throughout the experiment. In contrast, HDF10w was significantly heavier than SDF10w at 3, 4, 6, and 10 weeks of age (Fig. 1).

Imbalanced nutrition during pregnancy and lactation severely affects long-term irreversible outcomes in offspring owing to interference during a critical period of fetal growth. It has been suggested that pure genetics and epigenetics influence gene expression and the development of adverse effects in the offspring in later life. In mammals, the lactation period is an essential period for fetuses. An imbalance in nutrition in maternal milk could produce developmental programming effects that affect the offspring's health throughout life. Our results provide evidence that milk from high-fat diet-fed mothers influences and significantly increases the body weight of their offspring, as we observed in the HDM3w and HDF3w groups. The increased fat from the milk of the HD group could explain why pups in the HDM3w and HDF3w groups were significantly heavier than those in the SDM3w and SDF3w groups.

In offspring, the preference ratios for salty taste in the HDM10w and HDF10w groups were significantly higher than that in the SDM10w and SDF10w groups, respectively. There was no significant difference in the preference ratios for bitter, sour, sweet, and umami tastes (Fig. 2). Behaviorally, both HDM10w and HDF10w groups had a higher salty taste preference along with a higher body weight. A previous study suggested that increased activity in specific brain regions, which is related to taste sensation, food memory, and appetite, may be

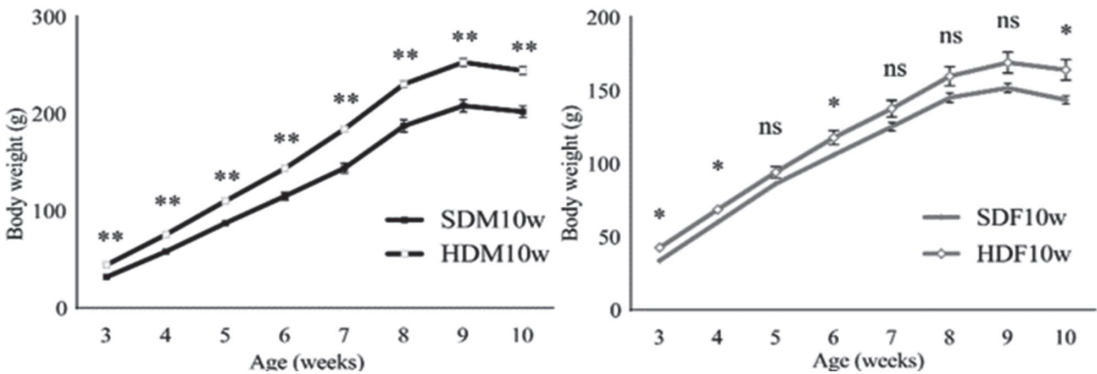


Fig. 1

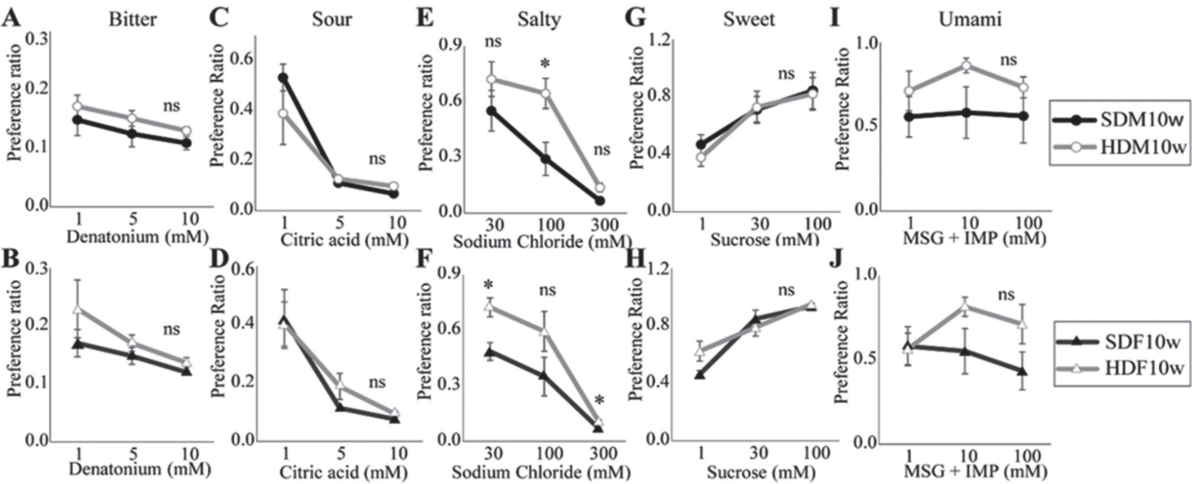


Fig. 2

one of the mechanisms contributing to the alteration of salty taste preference in obese patients.

The expressions of epithelial sodium channel alpha subunit (ENaC $\alpha$ ) and angiotensin II receptor type 1 (AT1) in the circumvallate papilla were analyzed by immunohistochemical (IHC) staining and reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Immunohistochemical staining revealed a high density of ENaC $\alpha$  immunoreactivity on the epithelial surface of the circumvallate papilla and lower density inside the taste bud cells of the SDM3w, SDF3w, HDM3w, and HDF3w groups. In contrast, AT1 was expressed in circumvallate taste buds but not in the epithelium. AT1 was predominantly expressed at the apical side of taste bud cells, which were close to the taste pore and in contact with the oral cavity environment. The area of AT1 immunoreactivity in the HDF3w group was more prominent than that in the SDF3w group. The semi-quantification of ENaC $\alpha$  and AT1 showed an increase in AT positive staining area in HDF3w compared to SDF3w. There was no significant difference among the other groups. (Fig. 3a, 3b)

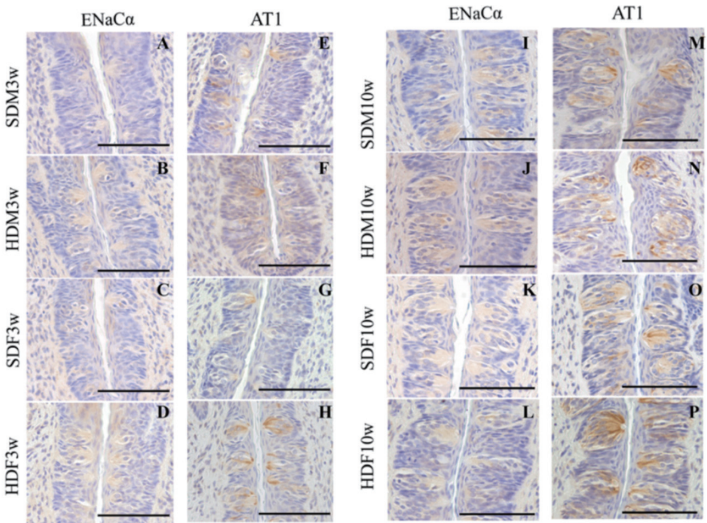


Fig. 3a

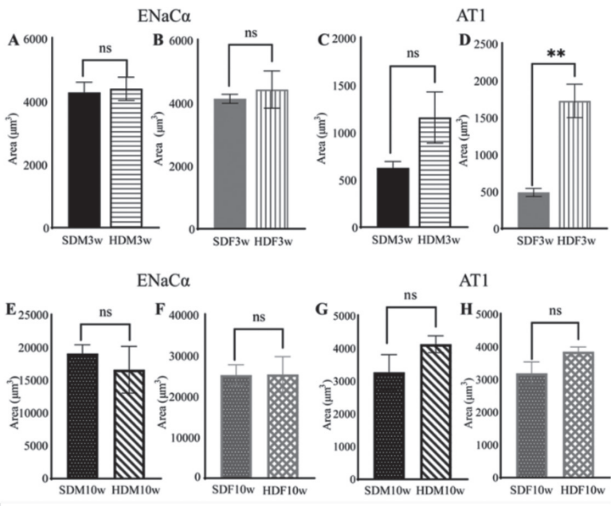


Fig. 3b

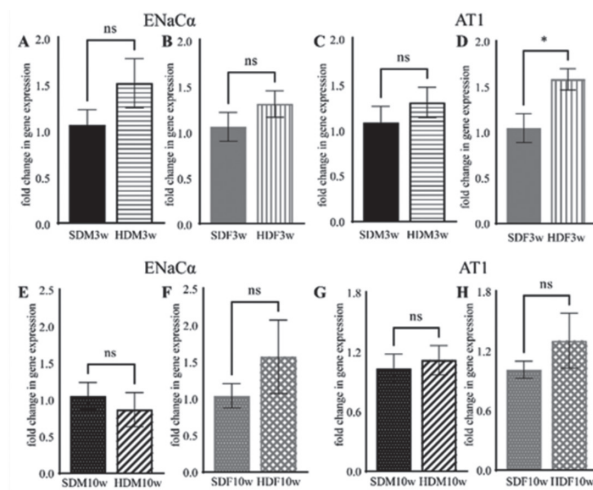


Fig. 4

The higher expression of AT1 in the HDF3w group at the age of 3 weeks could be a peripheral factor contributing to the increased salty taste preference in the HDF10w group (Fig. 4). Angiotensin II increases sodium intake via AT1 in taste cells. Correspondingly, an increased AT1 expression in the HDF3w, but not in the HDM3w, is consistent with the behavioral test results. A higher salt preference was exhibited at concentrations of 10 mM and 300 mM sodium chloride in the HDF10w group. In comparison, a higher salt preference was observed only at a specific 30 mM sodium chloride concentration in the HDM10w group.

In conclusion, maternal high-fat diet during pregnancy and lactation increased the expression of AT1 at weaning and behaviorally increased salty taste preference in rat offspring. Increased salty taste preference can lead to excessive sodium intake and exacerbate sodium homeostasis. Furthermore, alterations in the taste system are most likely to influence eating behavior. Unhealthy eating behavior in offspring increases the risk of lifelong systemic disorders.

**成果発表：**(予定を含めて口頭発表、学術雑誌など)

- 1) Saranya Serirukchutarungsee, Ippei Watari, Masataka Narukawa, Katarzyna Anna Podyma-Inoue, Pornchanok Sangsuriyothai, Takashi Ono. Two-generation exposure to a high-fat diet induces the change of salty taste preference in rats. Scientific Reports, in press.
- 2) Saranya Serirukchutarungsee, Ippei Watari, Masataka Narukawa, Katarzyna Anna Podyma-Inoue, Pornchanok Sangsuriyothai, Takashi Ono. Maternal high-fat diet in pregnancy and lactation period induces the change of taste preference in offspring. Annual Virtual Conference of the European Orthodontic Society, 2-3 July 2021