Dissimilarity in Fos and Jun Immunoreactivity in Hypothalamic Regions between Obese and Lean Zucker Rats

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The obese Zucker rat, whose genotype is transmitted in an autosomal recessive fashion, is an animal model widely used in the field of obesity. The expression of the nuclear transcription factors c-Fos and c-Jun in the paraventricular nucleus (PVN) and arcuate nucleus (ARC) of the hypothalamus of obese Zucker rats was studied using immunohistochemical methods. PVN and ARC in the hypothalamus are known as centers for the control of food intake. It was observed that the numbers of c-Fos-positive and c-Jun-positive neurons in these regions decreased in obese rats compared to lean rats, and that difference was more evident in the ARC than in the PVN which has to do with the regulation of body weight. The reduction in expression in the ARC of obese rats was greater for c-Jun than for c-Fos. These results suggest a possible difference in Fos immunoreactivity in hypothalamic resistance to circulating satiety factors in genetically obese Zucker rats.

Key words: obese Zucker rat; paraventricular nucleus; arcuate nucleus; c-Fos; c-Jun

Obesity can be influenced by both genetic and environmental factors in etiology.1,2 Excess caloric intake and decreased physical activity are some of the known environmental/behavioral causes of obesity.3 One of the most important factors causing extra fat deposition is altered autonomic neural activity, as found in obese animal models and humans.4–6 The Zucker rat is a strain of genetically modified obese rats whose traits appear spontaneously.7 It has been suggested that the obesity of the obese Zucker rat is due to resistance to circulating satiety factors induced in the hypothalamus,8 a well-recognized center for the regulation of food intake and energy homeostasis.9,10

In secretory neurons of the hypothalamic paraventricular nucleus (PVN), expression of the cellular transcription factors Fos and Jun, products of the immediate early genes (IEGs) c-fos and c-jun respectively, are induced in response to stress.10 The proto-oncogenes c-fos and c-jun are believed to play an important role in IEGs in the neurons. Their expression is rapidly induced by acute neuronal stimulation such as stress induced by fasting, and their peptide products are known to modulate the transcription rate of late genes.11,12 Lin and Huang11 reported that Fos immunoreactivity was increased in the PVN and ARC in lean and diet-induced obese mice when they were deprived of food. In a similar study, Fos immunoreactivity increased in the PVN and ARC in food-restricted rats compared to freely-fed rats.13 Also, Huang and Wang14 reported that hypothalamic Fos immunoreactivity increased in the brains of obese (ob/ob) mice.

The objective of this study was to determine the immunoreactivities of Fos and Jun, which are markers of neuronal activity, in the PVN and ARC of lean and obese Zucker rats using the immunohistochemical method.

The experiments were performed in accordance with the animal care guidelines of NIH and the Korean Academy of Medical Sciences. Adult male Zucker rats were housed in cages with alternating light-dark cycles...
observed in the PVN of the lean rats than in that of the obese rats. As was the case for Fos immunoreactivity, both lean and obese rats (Fig. 1E, F). As was the case for Jun immunoreactivity, more Jun-positive cells were observed in the PVN of the lean rats than in that of the obese rats. In the ARC, the regional predilection of Fos-positive cell expression appeared to be higher in the lean rats than in the obese rats. Statistical analyses of Fos and Jun-positive cells in the PVN and ARC of the lean and obese Zucker rats are shown in Table 1. The number of Fos-positive cells in the PVN and ARC of the lean rats was significantly higher than in the obese rats exhibiting 1.4 fold (p < 0.001 in PVN) and 1.7 fold (p < 0.05 in ARC) respectively. The numbers of Jun-positive cells in the PVN and ARC of the lean rats were also significantly larger than in the obese rats, by factors of 1.4 (p < 0.05 in PVN) and 2.4 (p < 0.001 in ARC) respectively.

Table 1. Numbers of Nuclei Immunopositive for Fos and Jun in the Hypothalamus of Obese and Lean Zucker Rats

<table>
<thead>
<tr>
<th></th>
<th>Fos-positive cells</th>
<th>Jun-positive cells</th>
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<tbody>
<tr>
<td></td>
<td>Lean</td>
<td>Obese</td>
</tr>
<tr>
<td>PVN</td>
<td>158.6 ± 5.3</td>
<td>112.3 ± 5.7**</td>
</tr>
<tr>
<td>ARC</td>
<td>59.0 ± 4.6</td>
<td>35.3 ± 2.1*</td>
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All data are presented as mean ± SEM.

*Significantly different from lean Zucker rats (p < 0.05).
**Significantly different from lean Zucker rats (p < 0.001).
PVN, paraventricular nucleus; ARC, arcuate nucleus.
A study by Lin and Huang found that environmentally induced obese mice demonstrated higher levels of Fos expression in the ARC than their lean counterparts, while those in the PVN were found to be similar. In addition, Huang and Wan have reported that hypothalamic Fos immunoreactivity increased in the brains of genetically obese mice. An earlier study by Drouin et al. reported an increase in Fos immunoreactivity among neurons in the PVN of genetically obese mice. It has been found that these obese mice feature increased appetite. Elevated neural activity in the brains of satiated obese mice might indicate the involvement of these neurons in stimulating food intake. In the present study, however, the genetically obese Zucker rats showed lower levels of c-Fos expression, in both the PVN and ARC, than the lean Zucker rats. It is interesting to note the results showing that decreases in the levels of expression of Fos and Jun in the obese rats were greater in the ARC, which is well-known for regulating the various aspects of body weight control, such as food intake and energy balance, than in the PVN. In addition, the reduction of expression in the ARC of the obese rats was greater for c-Jun than for c-Fos. From the results of this study, it is obvious that the level of Fos-positivity decreases in the obese Zucker rat, contrary to what has been observed in mice with hereditary or diet-induced obesity. This suggests the possible involvement of this difference in Fos immunoreactivity in hypothalamic resistance to circulating satiety factors, which have been proposed by others and appears to be a possible explanation for the obesity seen in the genetically obese Zucker rat.

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References


