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Involvement of Forebrain Glucose-monitoring Neurons in Taste Information Processing: Electrophysiological and Behavioral Studies

Zoltán Karádi[1], Balázs Lukáts[1], Szilárd Papp[1], Csaba Szalay[1], Róbert Egyed[1,2], László Lénárd[1] and Gábor Takács[1]

[1]Pécs University, Medical School, Institute of Physiology, Neurophysiology Research Group of the Hungarian Academy of Sciences (HAS), H-7601 Pécs, POB 99, Hungary

[2]Present address: Wyeth Hungary Ltd, H-1036 Budapest, Hungary

Correspondence to be sent to: Zoltán Karádi, e-mail: zoltan.karadi@aok.pte.hu

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Introduction

The ventromedial hypothalamic nucleus (VMH), the nucleus accumbens (NAcc) and the mediodorsal and ventrolateral prefrontal (orbitofrontal) cortices (mdPFC and OBF, respectively), key structures of the forebrain limbic circuitry, are known to play important roles in various mechanisms of the homeostatic regulation (Oomura, 1980; Swanson and Mogenson, 1981; Neafsey, 1990). In previous studies, special chemoneurons, the so called 'glucose-sensitive' (GS) and 'glucose-receptor' (GR) neural cells have been discovered in the above regions, and these glucose-monitoring (GM) neurons, in addition to specifically change in activity in response to increase of the extracellular glucose concentration, have also been shown to be involved in various processes of the organization of feeding (Oomura *et al.*, 1964; Oomura, 1980; Karádi *et al.*, 1995, 2002). Despite an increasing amount of related data, however, very little is known yet about simultaneous 'endogenous' and 'exogenous' gustatory chemosensitivities of these GM cells.

To elucidate the involvement of GM units in an integrative processing of complex chemical information, microelectrophysiological as well as behavioral investigations have been performed. Extracellular single neuron activity of the VMH, NAcc, mdPFC and OBF was recorded during (i) microelectrophoretic administration of D-glucose and other chemicals and (ii) gustatory stimulations as well. Recently conducted behavioral–biochemical experiments provided evidence for that the pancreatic β-cell destroying streptozotocin (STZ) (Like and Rossini, 1976) specifically damages the GM neurons if applied locally to these structures (Egyed *et al.*, 2000; Karádi *et al.*, 2000). In our other line of present studies, taste reactivity and taste associated learning ability were tested in STZ treated or control rats.

Materials and methods

Adult Wistar rats and rhesus monkeys (*Macaca mulatta*) of both sexes were used in these experiments. Tungsten wire multibarreled glass microelectrodes were manufactured by ourselves. Other technical details, such as operations, recording, microelectrophoresis, intraoral gustatory stimulations, etc. have already been described elsewhere (Karádi *et al.*, 1995).

The behavioral experiments included stereotaxic implantation of bilateral guide cannulae [stainless steel (ss), diameter 0.6 mm] above either of the targeted forebrain areas. After the full recovery of animals, steady microinjections of STZ (0.0037 M) or physiologic saline (0.15 M NaCl) via fine delivery cannulae (ss, diameter 0.3 mm) were achieved in hand-held, awake rats by means of a microinfusion pump (1 µl/min/side; 60 s waiting time after each administration). Taste reactivity by the method of Grill and Norgren (1978) and conditioned taste aversion (CTA) tests were performed one or two weeks after the intracerebral microinjections.

The appropriate brain atlases—Pellegrino *et al.* (1979) for the rat and Snider and Lee (1961) for the primate—were used for the stereotaxic manipulations and the histological examinations.

Analyses of data (with computation of means, standard errors, *F*-scores, Student's *t*- and χ^2-tests, ANOVA, paired comparisons) were performed as required.

Results

Single neuron recording

Activity changes of >450 neurons were recorded in these studies. Proportions of the GM cells varied from ~10% (mdPFC, OBF) and 14% (NAcc) to 30% (VMH) of all units tested. Only the excitatory type of cells (GR) was found in the VMH, whereas both types of GM neurons were identified in the other three areas. GS and GR units of the NAcc showed differential topographical organization, with the former being predominant in the 'shell' and the latter prevailing in the 'core' region.

A majority of the GM neurons in all the above forebrain structures also displayed responses to intraorally delivered taste stimuli. Figure 1 demonstrates activity changes of an accumbens GM cell to 'endogenous' and 'exogenous' chemical stimuli as well.

Chemoneurons of these brain areas, in addition to be modulated by glucose and gustatory stimuli, also changed in firing rate to various other (e.g. catecholamines), microiontophoretically administered chemicals.

Behavioral studies

A single bilateral STZ microinjection in these regions, in addition to leading to metabolic disturbances, resulted in the development of taste perception deficits. Alterations of taste reactivity were the most pronounced in case of treatment of the OBF (see Figure 2) or VMH. Characteristic taste aversion deficit was observed after STZ microinjection into the NAcc.

Discussion

The sense of taste plays multiple roles in feeding (Scott, 1992). Our present and previous data (Karádi *et al.*, 1995) demonstrate a close overlapping of the endogenous and exogenous chemosensory systems in the forebrain. In addition to their multiple endogenous humoral input, gustatory signals also converge on GM neurons whose hierarchically organized network system plays significant

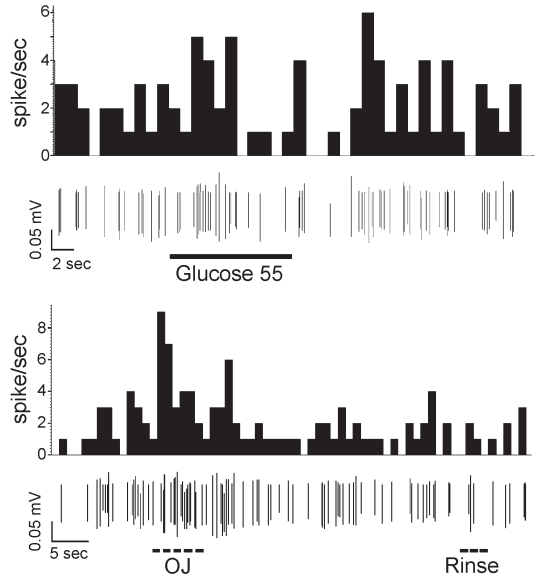

Figure 1 Firing rate changes of a GM neuron in the nucleus accumbens of the rat. Upper traces: microelectrophoretic administration of glucose elicited excitation–inhibition–excitation sequence of the cell. Lower traces orange juice (OJ) gustatory stimulation (dotted line) induced phasic facilitation of the same neuron. Thick horizontal bar, number, duration of the microelectrophoretic application and ejection current intensity in nA respectively.

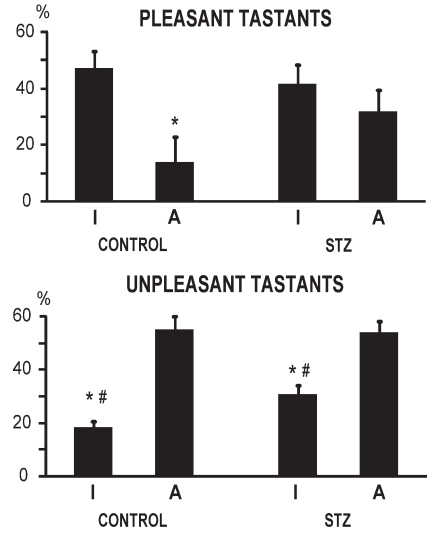

Figure 2 Taste reactivity alterations induced by bilateral streptozotocin microinjection into the orbitofrontal cortex of the rat. Arbitrarily evaluated behavioral responses to pleasant (upper) and unpleasant taste stimuli (lower) in streptozotocin treated (STZ, $n = 8$) versus control (CONTROL, $n = 8$) rats. I, A, ingestive and aversive patterns, respectively. $*\#P < 0.05$.

integrative roles in adaptive mechanisms of the central homeostatic control.

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