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Research Report

Glucose-monitoring neurons in the mediodorsal prefrontal cortex

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ABSTRACT

The mediodorsal prefrontal cortex (mdPFC), a key structure of the limbic neural circuitry, plays important roles in the central regulation of feeding. As an integrant part of the forebrain dopamine (DA) system, it performs complex roles via interconnections with various brain areas where glucose-monitoring (GM) neurons have been identified. The main goal of the present experiments was to examine whether similar GM neurons exist in the mediodorsal prefrontal cortex. To search for such chemosensory cells here, and to estimate their involvement in the DA circuitry, extracellular single neuron activity of the mediodorsal prefrontal cortex of anesthetized Wistar and Sprague–Dawley rats was recorded by means of tungsten wire multibarreled glass microelectrodes during microelectrophoretic administration of D-glucose and DA. One fourth of the neurons tested changed in firing rate in response to glucose, thus, proved to be elements of the forebrain GM neural network. DA responsive neurons in the mdPFC were found to represent similar proportion of all cells; the glucose-excited units were shown to display excitatory whereas the glucose-inhibited neurons were demonstrated to exert mainly inhibitory responses to dopamine. The glucose-monitoring neurons of the mdPFC and their distinct DA sensitivity are suggested to be of particular significance in adaptive processes of the central feeding control.

1. Introduction

The prefrontal cortex (PFC) is defined as the cortex of the anterior pole of the mammalian brain, predominantly receiving projections from the mediodorsal thalamic nucleus (Lacroix et al., 2000; Rose and Woolsey, 1948). It has been demonstrated that the prefrontal cortex is implicated in many regulatory processes, including cognitive functions, decision making, working memory, and the control of motivated behaviors such as the food and fluid intake (Baldwin et al., 2002; Cardinal et al., 2002; Heidbreder and Groenewegen, 2003; Kolb, 1984, 1990; Kolb and Nonneman, 1975; Morgane et al., 2005).

The prefrontal cortex is considered to perform its complex roles via multiple interrelationships with forebrain and brainstem areas. Anatomical studies have shown that the medial–mediodorsal prefrontal cortex (mdPFC) has direct connections with limbic structures, such as the amygdala (AMY), the lateral

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Abbreviations: AMY, amygdala; DA, dopamine; GM, glucose-monitoring; GR, glucose-receptor; GS, glucose-sensitive; LHA, lateral hypothalamic area; MB, methylene-blue; mdPFC, mediodorsal prefrontal cortex; NAcc, nucleus accumbens; NTS, nucleus of the solitary tract; OBF, orbitofrontal cortex; PFC, prefrontal cortex

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hypothalamic area (LHA), the nucleus accumbens (NAcc) and the adjacent orbitofrontal cortex (OBF) (Kita and Oomura, 1981; Kolb, 1984; Lacroix et al., 2000), all known to be important in the central feeding control. The rat mdPFC also directly projects to the nucleus of the solitary tract (NTS), a brainstem region which integrates a number of autonomic reflexes (Terreberry and Neafsey, 1987) and is well-known as a key structure of the central taste information processing (Norgren and Leonard, 1971; Rolls, 1989) as well.

In previous investigations, particular types of chemosensory cells, the so-called glucose-monitoring (GM) neurons – displaying firing rate changes in response to elevation of blood glucose level or to local microelectrophoretic administration of D-glucose – have been discovered in the above interconnected brain areas. Specific glucose-inhibited (glucose-sensitive, GS) neurons were identified in the LHA of rats (Oomura, 1980; Oomura et al., 1969) and later in the LHA and in the AMY of rhesus monkeys (Aou et al., 1984; Karadi et al., 1992; Nakano et al., 1986), and in the NTS, too (Adachi et al., 1984; Mizuno and Oomura, 1984). By contrast, the NAcc and the OBF were proven to contain not only GS cells but also glucose-excited (glucose-receptor, GR) neurons that are facilitated by increase of the extracellular glucose concentration (Karadi et al., 2004; Papp et al., 2007).

The GM cells were demonstrated to be influenced by catecholamines (Karadi et al., 1992, 2004; Lenard et al., 1995), and with respect to this it is especially important to note that the PFC is the major cortical target area of the ascending dopamine (DA) projections (Berger et al., 1976; Björklund and Lindvall, 1984; Descarries et al., 1987; Ungerstedt, 1971). In addition to responding to endogenous chemical stimuli, these chemosensory neurons, forming a hierarchically organized neural network, are also known to integrate multiple, homeostatically relevant information, such as exogenous chemical and other signals, sensory-motor, perceptual, motivational mechanisms, as well as reinforcement, learning and memory processes, to control feeding and metabolic functions (Aou et al., 1984; Karadi et al., 1992, 1995, 2004; Oomura and Yoshimatsu, 1984).

Considering the above, it is supposed that the mediodorsal prefrontal cortex accomplishes its complex roles as integrant part of the forebrain glucose-monitoring neural network. In the present experiments, therefore, we aimed to identify GM neurons in the mdPFC, and to examine their responsiveness to DA. To do so, extracellular single neuron activity was recorded in the mdPFC of anesthetized male Wistar and Sprague–Dawley rats, by means of tungsten wire multibarreled glass microelectrodes during microelectrophoretic application of D-glucose and dopamine.

2. Results

Activity changes of altogether 272 neurons have been recorded in the Wistar and Sprague–Dawley rat mdPFC. The mean spontaneous firing rates were 2.2±0.2 and 2.4±0.3 spikes/s, respectively, and did not vary significantly between the two preparations. To examine direct neuronal effect of glucose, single neuron activity was recorded during microelectrophoretic administration of D-glucose. Results of the neurochemical stimulations are summarized in Table 1. Sixty-two (24.3%) of 255 mdPFC neurons showed responsiveness to glucose, thus, these cells were found to be elements of the forebrain GM neural network. The predominant response to glucose was inhibition (43 of the 62 GM neurons, 69.4%), however, definite facilitatory activity changes were also detected (19 /30.6%/ of the 62 neurons). The other 193 neurons (75.7%) did not change in firing rate to glucose and thus, were classified as glucose-insensitive (GIS) cells.

Table 1 – Effect of microelectrophoretically applied glucose and dopamine on rat mdPFC neurons.

	Glucose	DA
↑	19	28
↓	43	27
Ø	193	180
Total	255	235

↑: Excitatory response; ↓: inhibitory response; Ø: no response.

DA responsiveness of 235 cells was examined in the rodent mdPFC. Microiontophoretic application of DA resulted in activity changes of 55 neurons (23.4%). As Table 1 shows, in the case of DA administration, the proportion of excitatory (28, 11.9%) and inhibitory (27, 11.5%) responses was almost the same.

Table 2 demonstrates distinct DA responsiveness of glucose-monitoring and glucose-insensitive neurons in the mdPFC. Twenty-one (41.2%) of the 51 GM units, whereas only 27 (16.2%) of the 167 GIS neurons displayed discharge rate changes to this neurotransmitter, so that DA responsiveness of the GM cells was found to be significantly higher than that of the glucose-insensitive units ($p<0.001$; χ^2 test). DA elicited only excitatory response in the GR cells (7 of 15 neurons, 46.7%), whereas both inhibitory (10 of 36 units, 27.8%) and excitatory (4 of 36 cells, 11.1%) firing rate changes were observed in the GS neurons. Consequently, direction of the DA induced activity changes of the two types of GM cells differed significantly ($p<0.01$; χ^2 test). Discharge rate changes of two characteristic DA responsive GM cells in the mdPFC are shown in Fig. 1.

The magnitude of the response to microelectrophoretically administered glucose and DA was also examined. Fig. 2 demonstrates the size of the ejection current-dependent responses of mdPFC neurons. Both in case of glucose and

Table 2 – DA responsiveness of GM and GIS neurons in the rat mdPFC.

	DA↑	DA↓	DAØ	Total
GR	7*	0	8	15
GS	4	10*	22	36
GIS	15	12	140	167
Total	26	22	170	218

GIS: glucose-insensitive neuron; GR: glucose-receptor neuron (excited by D-glucose); GS: glucose-sensitive neuron (inhibited by D-glucose); DAØ: DA-nonresponsive neurons; DA↑: neurons facilitated by DA; DA↓: neurons inhibited by DA.

* $P<0.001$ (χ^2 test).