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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).

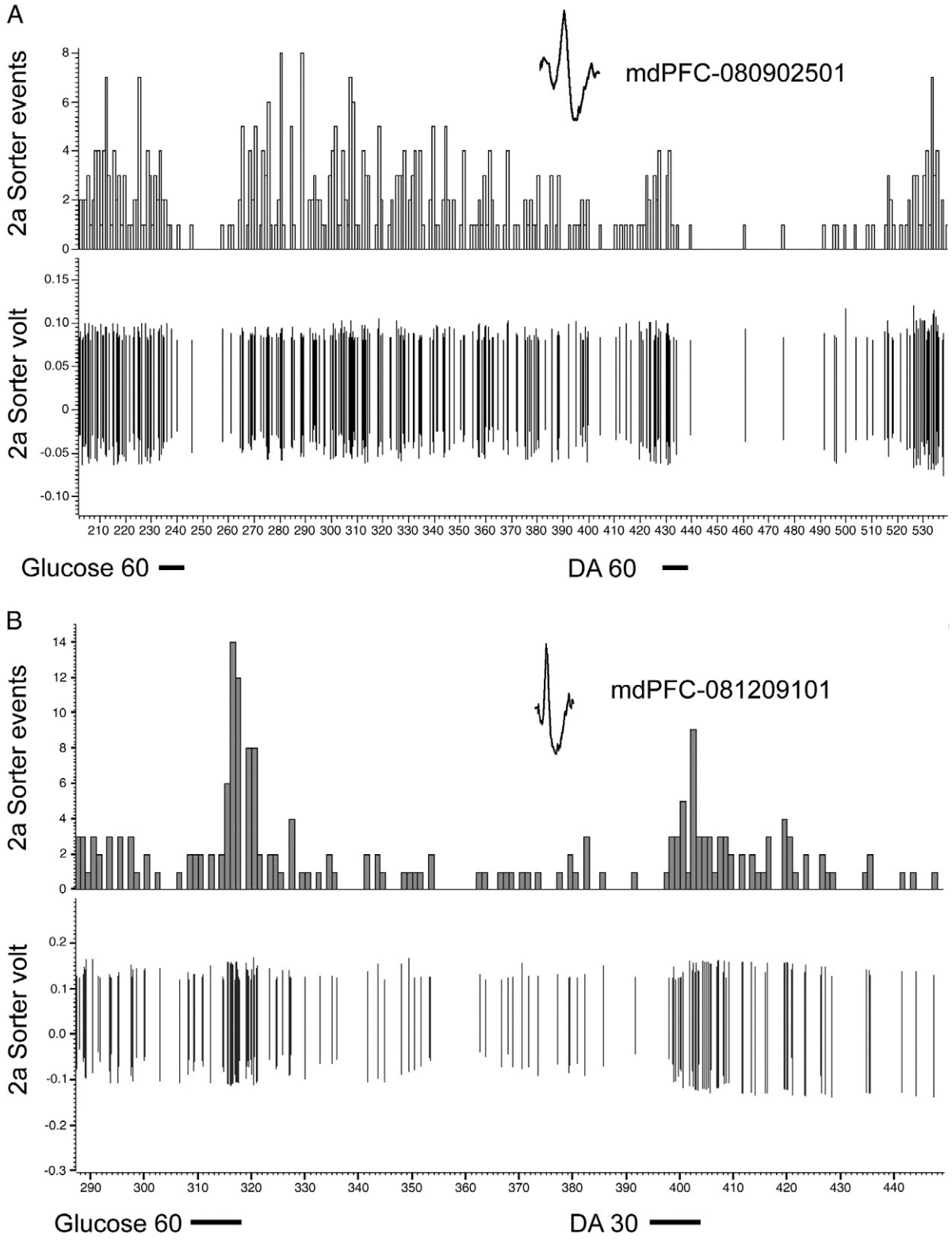

Fig. 1 – Responses of two mdPFC neurons to microelectrophoretically applied D-glucose and dopamine. A, a glucose-sensitive cell inhibited by D-glucose and DA; B, a glucose-receptor neuron facilitated by D-glucose and dopamine. Spike insets, characteristic action potentials. Horizontal lines, numbers, duration of drug application and ejection current intensities in nA, respectively. Abscissa, time in s; ordinate, firing rate in spikes/s and potential in mV, respectively.

dopamine administrations, higher current intensities resulted in significantly bigger firing rate changes of cells of the responsive groups ($p<0.05$, Wilcoxon test).

Analysis of other electrophysiological characteristics revealed additional functional attributes of the neurons. As Fig. 3 represents, the baseline firing rates and spike durations

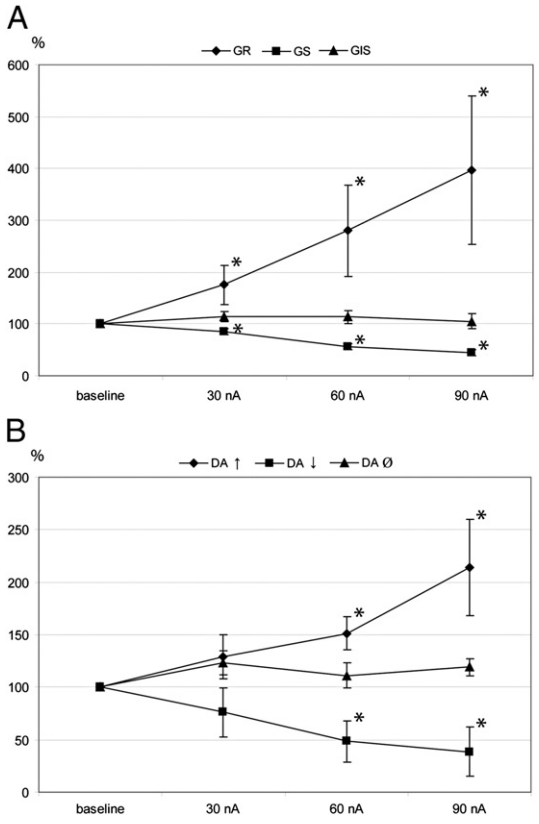

Fig. 2 – Current response curves showing the magnitude of the response (mean ± SEM) in percentage of baseline firing for 3 representative current intensities (30 nA, 60 nA, 90 nA, respectively). GR: glucose-receptor cells, GS: glucose-sensitive cells, GIS: glucose-insensitive cells; DA ↑: neurons facilitated by DA; DA ↓: neurons inhibited by DA; DA Ø: DA-insensitive neurons. *p < 0.05, Wilcoxon test.

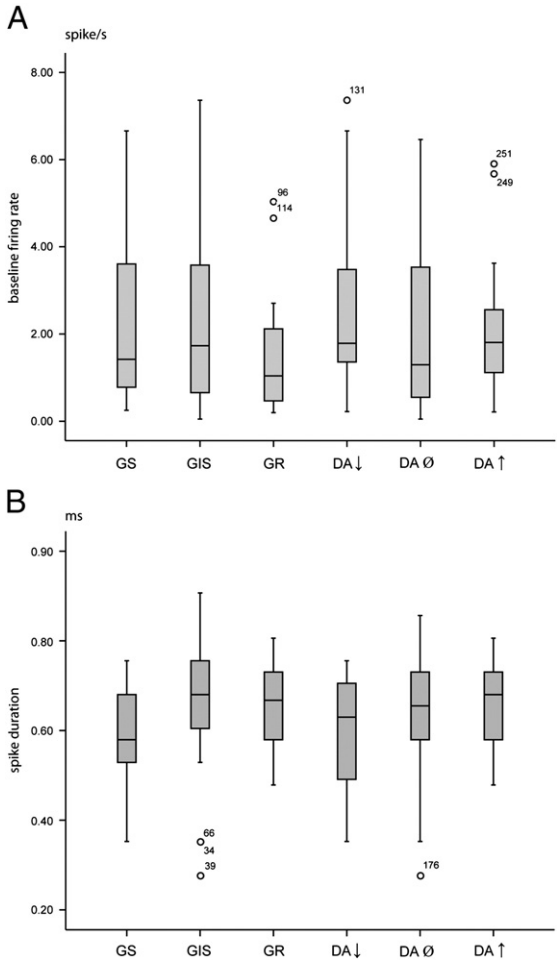

Fig. 3 – Box diagrams of distribution of baseline firing rates (A) and spike durations (B) of the various cell groups examined. The duration of the spikes was measured between the negative trough and the positive peak of the spike waveforms. Numbered open circles refer to neurons out of the continuous data range. Abbreviations are identical with those in Fig. 2.

of the cells with various glucose and DA responsiveness did not show significant difference ($p = 0.248$ and $p = 0.30$, respectively; Kruskal–Wallis test). In addition, neither baseline firing rates nor spike durations were found to correlate with glucose or dopamine responses ($p \geq 0.213$).

Burst firing characteristic of the neurons was also examined. We have found the most burst firing cells among the neurons inhibited by DA (64.3%), and the fewest ones (17.6% and 15%, respectively) among the cells facilitated by this catecholamine as well as among those excited by glucose ($p < 0.05$; χ^2 test).

As far as the location of the cells characterized by distinct neurochemical sensitivities is concerned, their topography appeared to be similar, the various neurons were found to be quite homogenously and overlappingly distributed within the mdPFC.

3. Discussion

Results of these experiments provided evidence for the presence of glucose-monitoring neurons in the mediodorsal prefrontal cortex. Although such feeding-associated chemosensory neurons have already been identified in several other brain regions (Adachi et al., 1984; Aou et al., 1984; Karadi et al., 1992, 2004; Mizuno and Oomura, 1984; Nakano et al., 1986; Oomura, 1980; Oomura et al., 1969; Papp et al., 2007), this is the first systematic study to demonstrate their existence in this cortical division of the forebrain limbic circuitry. The mdPFC is known to be involved in a broad variety of regulatory processes, and its important role in the central feeding control has been demonstrated as well (Cardinal et al., 2002; Kolb, 1984; Kolb and Nonneman, 1975; Mogensen and Divac, 1993). Since GM neurons of several brain areas have already been shown to be indispensable constituents of integration of endogenous and exogenous chemical information, sensory-motor integration, perceptual and motivational processes, as well as reinforcement, learning and memory mechanisms of the regulation of food and fluid intake behaviors (Aou et al., 1984; Karadi et al., 1992, 1995, 2004; Lenard et al., 1995; Oomura and Yoshimatsu, 1984; Oomura et al., 1969; Papp et al., 2007), it is reasonable to suppose that these chemosensory cells of the mdPFC possess similar complex functional attributes in the organization of adaptive feeding actions. It is important to note that the former results have been obtained predominantly in the macaques whereas the present

study was performed in the rodent. Nevertheless, findings of the latter gain more general significance in the light of our most recent microelectrophysiological experiments in the alert rhesus monkey revealing that GR and GS neurons also exist in the primate mdPFC (unpublished data).

As the other major finding of the present experiments, distinct dopamine sensitivity of the mdPFC neurons has been elucidated: the feeding-associated GM units were shown to be more likely to change in activity in response to microiontophoretically administered DA than the glucose-insensitive cells. Furthermore, the GR neurons were found to get facilitated whereas the GS units mainly inhibited by this catecholamine. These data are in concordance with previous results demonstrating higher dopamine responsiveness of the lateral hypothalamic and pallidal GM neurons compared to that of the GIS cells, as well as the predominance of DA induced inhibitory firing rate changes of the GS neurons in the LHA (Karadi et al., 1992; Lenard et al., 1995).

The dense dopaminergic innervation of the PFC (Berger et al., 1976; Björklund and Lindvall, 1984; Descarries et al., 1987; Ungerstedt, 1971) has already been indicated to play important roles in a variety of regulatory processes (Dalley et al., 2004; Goeders et al., 1986; Granon et al., 2000; Hedou et al., 1999; Ikemoto, 2010; Richardson and Gratton, 1998; Tzschentke, 2001), including feeding-associated and taste mediated learning and memory mechanisms as well (Baldwin et al., 2002; Gambarana et al., 2003; Hernadi et al., 2000; Touzani et al., 2010). It is especially worth noting here that food intake itself or stimuli associated with the food have been demonstrated to increase the extracellular DA concentration in the prefrontal cortex (Bassareo and Di Chiara, 1997; Hernandez and Hoebel, 1990). These and our present data are also in agreement with the notion that multiple regulatory functions of the mdPFC are perfectuated via interrelated complex neurochemical mechanisms (Morgane et al., 2005; Tzschentke, 2001).

The prefrontal cortical GM neurons are suggested to participate in the integration of several homeostatically relevant endogenous and exogenous signals. The chemosensory neurons at this high decision making level of the neuraxis, by utilizing their differential dopamine sensitivity, are supposed to play significant role in the control of adaptive behavioral actions for the well being of the organism.

Previous recording studies have suggested that cortical interneurons have briefer spikes than those of pyramidal neurons, though cortical pyramidal neurons may exhibit a wide variety of spike durations (Bartho et al., 2004; Contreras, 2004; Vigneswaran et al., 2011). In our study, examination of spike durations revealed no significant difference among the various groups of neurons, and spike durations also did not correlate

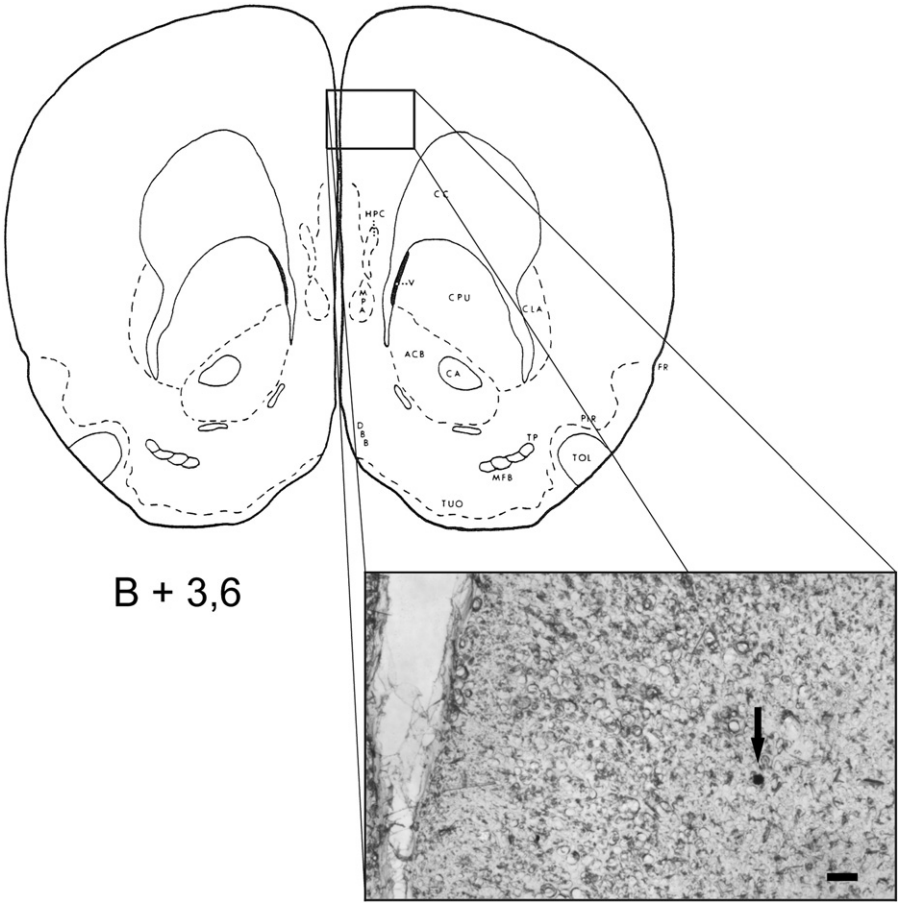

Fig. 4 – Drawing of a brain section from the stereotaxic rat atlas (Pellegrino et al., 1979) at the level of the mediodorsal prefrontal cortex (the number refers to the anteroposterior coordinate with reference to bregma). Inset, photomicrograph of a native brain section with the microelectrophoretic methylene blue labeling spot (pointed by arrow) of a representative glucose-monitoring neuron; scale bar, 100 μm.

with glucose and dopamine responses. Relationship appears to exist, however, between neurochemical sensitivity of neurons and their burst firing characteristics: the most burst firing cells were found among the neurons inhibited by DA, whereas the fewest burst firing cells were observed among the cells facilitated by glucose and/or the catecholamine.

To understand the significance of these above findings, and to elucidate details of complex functional attributes of the mediodorsal prefrontal cortical glucose-monitoring neurons, including their DA receptor mechanisms, further studies are required.

4. Experimental procedures

Thirty-seven Wistar, and fifteen Sprague–Dawley male laboratory rats (weighing 305–380 g) were used in these experiments. Individually caged animals were kept and cared for in accordance with institutional, national and international regulations (BA02/2000-1/2006, Pécs University, Medical School; Law XXVIII, 1998, Hungary; European Community Council Directive 86/609/EEC, 1986, 2006; NIH Guidelines, 1997). Anesthesia was induced with a single injection of urethane (0.6 ml/100 g body weight, 25% fresh solution, Sigma, Hungary). Rats were operated on stereotaxically, their scalp was incised, and a small hole was drilled through the skull. The microelectrode was led to the mdPFC under microscopic control through the incised dura by means of a hydraulic microdrive (Narishige MO-10, Japan). The stereotaxic coordinates for electrode placements in the mdPFC were chosen according to the rat brain atlas (Pellegrino et al., 1979): anteroposterior, bregma + 3.2–4.0 mm; mediolateral, 0.7–1.6 mm; vertical, 0.6–2.8 mm. Extracellular recording and microelectrophoretic application of neurochemicals were accomplished by means of nine-barreled glass microelectrodes. Single-neuron activity was recorded via the central barrel containing a tungsten wire (10 μm in diameter, impedance 1.5–8 MΩ at 50 Hz). Neurochemicals were applied electrophoretically through the capillaries surrounding the central recording electrode. Each barrel was filled with one of the following solutions: D-glucose (0.5 M, pH 7.0), dopamine hydrochloride (0.5 M, pH 6), and monosodium L-glutamate (0.5 M, pH 7–8; to test the electrode tip's vicinity to the recorded neuron). In addition to the above, one barrel was filled with physiological saline used as a current balancing channel, and another one with methylene-blue (MB, Reanal Ltd., Hungary) for labeling the position of the electrode's tip. Constant current source (NeuroPhore BH-2 System, USA), producing constant currents (in the 5–95 nA range) of appropriate polarity, was applied to eject the neurochemicals from their respective barrels. Extracellular action potentials were passed into a preamplifier, a high gain amplifier including low and high cut filters and a window discriminator to form standard pulses (Supertech Ltd., Hungary), and then into a microprocessor controlled A/D converter device (CED 1401 plus). The Spike 2 software package (Cambridge Electronic Design Ltd., United Kingdom) was used to construct frequency histograms and for real-time and off-line analyses. Neuronal spikes and formed pulses were continuously observed on oscilloscopes (HAMEG HM-2037, Germany). Only the action potentials of spontaneously active, well-isolated cells were recorded. Neurons that showed non-specific current effects (response to Na^+ or Cl^- ions) were excluded from the analysis.

Similar to our previous studies, a neuron was considered to be responsive to a certain neurochemical if its firing rate changed by at least ±30% or by ±2 SD from the mean baseline level, and if the reactions were dose dependent (by using different current intensities), and replicable.

For statistical analysis of the data, the Wilcoxon test, Kruskal–Wallis test, linear regression test, and χ^2 test were used.

In addition to the stereotaxic determination of the electrode position, recording sites were marked by methylene-blue (MB) labeling and confirmed by subsequent histological examination. Accordingly, anodal labeling current (50 nA, 10–15 min) was delivered through the MB containing barrel at the end of the recording sessions (Kovacs et al., 2005). After completion of the marking procedure, rats were perfused transcardially with physiological saline followed by paraformaldehyde (4%) and the brains were postfixed overnight in paraformaldehyde. After PBS rinsing, native sections were cut for light microscopic identification of the recording sites (see representative photomicrograph in Fig. 4).

5. Conclusion

Our results provided evidence for the existence of special chemosensory neurons in the mediodorsal prefrontal cortex. The differential dopamine responsiveness of these GS and GR cells is suggested to be of distinguished importance with respect to their complex roles in the central regulation of food and fluid intake behaviors.

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