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Research Report

Noradrenaline and acetylcholine responsiveness of glucose-monitoring and glucose-insensitive neurons in the mediodorsal prefrontal cortex

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ABSTRACT

The mediodorsal prefrontal cortex (mdPFC), as part of the forebrain glucose-monitoring (GM) system, plays important role in several regulatory processes to control the internal state of the organism and to initiate behavioral outputs accordingly. Little is known, however, about the neurochemical sensitivity of neurons located in this area. Substantial evidence indicates that the locus ceruleus – noradrenaline (NA) projection system and the nucleus basalis magnocellularis – cholinergic projection system regulate behavioral state and state dependent processing of sensory information, various cognitive functions already associated with the mdPFC. The main goal of the present study was to examine noradrenergic and cholinergic responsiveness of glucose-monitoring and glucose-insensitive (GIS) neurons in the mediodorsal prefrontal cortex. One fifth of the neurons tested changed in firing rate to microelectrophoretically applied NA. Responsiveness of the GM cells to this catecholamine proved to be significantly higher than that of the GIS units. Microiontophoretic application of acetylcholine (Ach) resulted in activity changes (predominantly facilitation) of more than 40% of the mdPFC neurons. Proportion of Ach sensitive units among the GM and the GIS neurons was found to be similar. The glucose-monitoring neurons of the mdPFC and their distinct NA and remarkable Ach sensitivity are suggested to be of particular significance in prefrontal control of adaptive behaviors.

1. Introduction

The prefrontal cortex (PFC) plays important role in many regulatory processes, including cognitive functions, attention, 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; Dalley et al., 2004; Heidbreder and Groenewegen, 2003; Kolb and Nonneman, 1975; Kolb, 1984, 1990; Morgane et al., 2005). The prefrontal cortex performs its complex roles via multiple interrelationships with forebrain and

Abbreviations: NA, noradrenaline; Ach, acetylcholine; DA, dopamine; GM, glucose-monitoring; GIS, glucose-insensitive; MB, methylene-blue; mdPFC, mediodorsal prefrontal cortex; PFC, prefrontal cortex; LC, locus ceruleus; NBM, nucleus basalis magnocellularis

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brainstem areas (Kolb, 1984). Our previous results showed that one fourth of the neurons in the mediodorsal prefrontal cortex (mdPFC) changed in firing rate in response to glucose, thus, these cells proved to be elements of the central glucose-monitoring (GM) neural network (Nagy et al., 2012a). Constituents of this hierarchically organized network (hypothalamus, amygdala, nucleus accumbens, globus pallidus, orbitofrontal cortex, mdPFC) integrate neurochemical and other signals from the periphery, from the local brain milieu and signals arriving via projections from other brain areas (Aou et al., 1984; Karadi et al., 1992, 2004; Lénárd and Karádi, 2012; Oomura et al., 1969; Papp et al., 2007).

Several neuromodulatory pathways converge in the mPFC, among others, the locus ceruleus (LC) – noradrenaline (NA) projection system and the nucleus basalis magnocellularis (NBM) – cholinergic projection system (Chandler and Waterhouse, 2012; Condes-Lara, 1998; Porrino and Goldman-Rakic, 1982) as well. The LC is the primary source of noradrenergic innervation of the forebrain and the PFC (Berridge and Waterhouse, 2003; Chandler and Waterhouse, 2012) in it. This cortical area has been demonstrated to play important role in the modulation of sensory processing, arousal, cognitive and other behavioral processes (Aston-Jones and Cohen, 2005; Devilbiss and Waterhouse, 2004; Devilbiss et al., 2006). A variety of appetitive and aversive stimuli elicit increases in LC discharge activity, and increased NA output from the LC is reportedly correlated with enhanced transmission of sensory signals. The NA release increases the ability to process relevant or salient stimuli – via actions on sensory, attention, memory and motor processes – while suppressing responses to irrelevant stimuli (Berridge and Waterhouse, 2003).

Electrophysiological and lesion analysis studies support the hypothesis that acetylcholine (Ach) is also important in significance associated evaluation of sensory information, and this “classic” neurotransmitter was also shown to improve the “signal-to-noise” ratio of the incoming sensory information (Sarter and Bruno, 2000; Wenk, 1997; Wilson and Rolls, 1990a, 1990b). The NBM cholinergic system is supposed to be involved in the control of attention processes, such as the control of shifting attention towards potentially more important sensory stimuli that predict biologically relevant events, such as, e.g. the availability of food reward.

Considering the above, it is proposed that the mediodorsal prefrontal cortex, as integral part of the forebrain glucose-monitoring neural network, accomplishes its complex roles by means of, at least in part, the integration of its noradrenergic and cholinergic inputs. In the present experiments, therefore, we aimed to examine the impact of noradrenaline and acetylcholine on the discharge rate of mdPFC neurons. To identify GM neurons here, and to estimate their modulation by the NA and Ach circuitries, the 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 microiontophoretic administration of D-glucose, NA and Ach.

2. Results

Activity changes of altogether 230 neurons have been recorded in the Wistar and Sprague-Dawley rat mdPFC. The mean spontaneous firing rates in the two strains were 2.2 ± 0.2 and 2.3 ± 0.3 spikes/s, respectively. Noradrenaline and acetylcholine responsiveness of mdPFC neurons was examined during microiontophoretic administration of these neurotransmitters. Results of the neurochemical stimulations are summarized in Table 1. Thirty-seven (18.4%) of 201 mdPFC cells showed responsiveness to NA. The proportion of excitatory (19, 9.4%) and inhibitory (18, 8.9%) activity changes was almost the same.

Ach responsiveness of 177 cells was examined in the rodent mdPFC. Microiontophoretic application of Ach resulted in firing rate changes of 75 neurons (42.4%). The predominant response to this neurotransmitter was facilitation (65 of the 75 Ach-sensitive neurons, 86.7%), however, definite inhibitory activity changes were also detected (10/13.3%/ of the 75 neurons).

Table 2 demonstrates distinct NA responsiveness of glucose-monitoring and glucose-insensitive (GIS) neurons in the mdPFC. Nineteen (46.3%) of the 41 g units, whereas only 18 (11.2%) of the 160 GIS neurons displayed discharge rate changes to this neurotransmitter, so that NA responsiveness of the GM cells was found to be significantly higher than that of the glucose-insensitive units ($p < 0.001$; χ^2 test). Results of the Ach administrations are summarized in Table 3. The proportion of Ach-responsive GM (45.1%) and GIS neurons (41.7%) proved to be almost the same. Majority of the individual glucose-monitoring and glucose-insensitive cells were tested for sensitivity to both NA and Ach (Table 4). Firing rate changes of two characteristic mdPFC neurons responding to various neurochemicals are shown in Fig. 1.

The ejection current-dependent response characteristics to the micro-electrophoretically administered NA and Ach are demonstrated in Fig. 2. Higher current intensities resulted in significantly larger firing rate changes of cells of the responsive groups in the case of both neurotransmitters ($^{*}p < 0.05$, $^{\#}p < 0.001$, Wilcoxon test).

As far as the topographic location of the NA and Ach-responsive units within the mdPFC is concerned, similar to the topography of the GM neurons (Nagy et al., 2012a), the various types of neurons with characteristic neurochemical sensitivities were found to be quite homogenously distributed within the examined area in both rat strains.

3. Discussion

Data obtained in the current experiments provided evidence for the NA and Ach sensitivity of glucose-monitoring neurons in the mdPFC. Although these feeding-associated chemosensory neurons have already been identified in several other brain regions, and the majority of these cells were shown to

Table 1 – Effect of microelectrophoretically applied noradrenaline and acetylcholine on rat mdPFC neurons.

	Noradrenaline	Acetylcholine
↑	19	65
↓	18	10
Ø	164	102
Total	201	177

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