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Single unit activity in the medial prefrontal cortex during pavlovian heart rate conditioning: Effects of peripheral autonomic blockade

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Abstract

Electrical activity was recorded from single neurons in the medial prefrontal cortex of rabbits during differential Pavlovian heart rate (HR) conditioning. A heterogenous population of cells were found, some of which showed CS-evoked increases and others CS-evoked decreases in discharge, while some cells were biphasic. A subset of cells also showed trial-related changes in discharge that were related to acquisition of the HR discrimination between the reinforced CS+ and non-reinforced CS−. Administration of the peripheral cholinergic antagonist, methylscopolamine, and the andrenergic antagonist, atenolol, either increased or decreased maintained baseline activity of many cells, but had little or no effect on the CS-evoked activity of these cells. Waveform changes also did not result from administration of these drugs. This finding suggests that CS-evoked mPFC activity is not being driven by cardiac afferent input to CNS cardiac control centers. Previous studies have shown that ibotenic acid lesions of this area greatly decreases the magnitude of decelerative heart rate conditioned responses; the latter finding, plus the results of the present study, suggest that processing of CS/US contingencies by the prefrontal cortex contributes to the acquisition of autonomic changes during Pavlovian conditioning.

Keywords: Rabbits; Methylscopolamine; Atenolol; Autonomic blockade; Learning

1. Introduction

It has been suggested that the prefrontal cortex (PFC) integrates emotional memories with sensory and motor memories to regulate sensory information and plan behavior (Damasio, 1999; Goel, Grafman, Tajik, Gana, & Danto, 1997). Thus, the PFC may attach emotional significance to remembered facts, so that feelings evoked by a particular event are recalled with memory for that event, in order that emotions occur during a specific context. Thus, patients with frontal lobe damage typically express dysfunctional emotions, which may interfere with reasoning and may relate to the maladaptive behaviors observed (Damasio, 1999; Fuster, 1997).

This emotional learning component, which is impaired in humans with PFC damage, may be indexed by the autonomic component of associative learning, exhibited by animals, as well as people during Pavlovian conditioning (Powell, 1999; Powell, McLaughlin, & Chachich, 2000). Recent research using animal models have investigated the role of the PFC in regulating learned autonomic adjustments, which are presumed to index emotional processing in animals. For example, lesions of the anterior cingulate (Brodmann's area 24) and prelimbic cortex (Brodmann's area 32) attenuate conditioned bradycardia during aversive eyeblink (EB) conditioning in restrained rabbits (Buchanan & Powell, 1993; Powell, 1999; Powell, Watson, & Maxwell, 1994). Moreover,

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infralimbic (area 25) lesions attenuate conditioned tachycardia and pressor responses in freely moving rats (Frysztak & Neafsey, 1991, 1994). However, neither EB nor jaw movement (JM) somatomotor conditioning is disrupted by PFC lesions (Buchanan & Powell, 1982; McLaughlin & Powell, 1999; Powell, 1994; Powell, Gibbs, Maxwell, & Levine-Bryce, 1993), although the accompanying HR response is severely depressed. Electrical stimulation studies are compatible with the lesion studies, in suggesting that area 24 and area 32 mediate the parasympathetic changes that occur during Pavlovian conditioning (Neafsey, Hurley-Guis, & Arvanitis, 1986; Powell, 1994). Electrophysiological recording studies have found that conditioned stimulus (CS) evoked activity of single cells in the medial prefrontal cortex (mPFC) was related to the magnitude of concomitant, CS-evoked changes in HR (Gibbs & Powell, 1991; Maxwell, Powell, & Buchanan, 1994). The majority of these cells showed CS-evoked increases in discharge, but some showed CS-evoked decreases as well. These recording studies thus suggest that neural activity in the mPFC contributes significantly to the development and/or expression of learned cardiovascular adjustments in the rabbit (Gibbs, Prescott, & Powell, 1992).

Although single unit output was associated with the conditioned HR changes elicited in the above electrophysiological studies, it was impossible from these data to determine, if or whether, such changes were related to actual acquisition of the HR CR, since these recordings were made during extinction after training was complete (Gibbs & Powell, 1991; Maxwell et al., 1994). This procedure was necessary, because it is difficult to record from a single cell over successive trials due to head movement produced by the presentation of the periorbital shock unconditioned stimulus, even though the animal's head is restrained, since the electrode is acutely lowered into the brain. In the present study a different method was employed that allows the recording of multiple unit activity from fine wires resting in the brain and the offline separation of single units from such activity over trials so that acquisition of behavioral change can be assessed. This technology was employed in the present study to assess whether discharge of mPFC neurons change as a function of acquisition trials.

A second question asked in the present experiments was whether peripheral autonomic blockade, which would interfere with normal sympathetic and vagal influences on the heart would influence correlated mPFC neuronal activity. This experiment was motivated by the question of whether CS-evoked changes in discharge of mPFC cells is produced by peripheral afferent activity from the heart induced by the cardiac changes that occur during conditioning. Vagal afferents, for example, are known to reach prefrontal areas (Bailey & Bremer, 1938; Encabo & Ruarte, 1967). Thus, mPFC discharge in response to the conditional stimulus could be driven by these afferents. The alternative hypothesis, of course, is that such mPFC neuronal activity is causally related to the cardiac changes produced by the conditioning contingencies. The lesion data described above would suggest that the latter is the case. Nevertheless, to test the former hypothesis, in a second experiment single unit activity was assessed in animals after the administration of either saline, methylscopolamine, or atenolol, to determine whether mPFC activity would be affected by peripheral administration of these pharmacological agents.

2. Experiment 1

2.1. Materials and methods

2.1.1. Animals

New Zealand albino rabbits (8 males and 9 females), approximately 6 months of age were obtained from a local supplier licensed by the United States Department of Agriculture (USDA) (Robinson Services, Winston Salem, NC). The rabbits were individually housed in an animal facility accredited by the American Association for Assessment and Accreditation of Animal Laboratory Care International. The animals were subjected to a 12-h light: 12-h dark cycle (lights on at 07:00 h in the morning) with food and water available ad libitum. All animals were studied during the daylight portion of the light/dark cycle. Care and use of the animals followed the guidelines outlined by the US Public Health Service and the US Department of Veterans Affairs.

2.1.2. Surgery

Surgery was performed using aseptic conditions, under general anesthesia, using a combination of ketamine hydrochloride (55 mg/kg, i.m.), acepromazine maleate (2.2 mg/kg, i.m.), and xylazine (4.4 mg/kg, i.m.). The rabbit was positioned in a Kopf stereotaxic instrument, equipped with a rabbit head holder. A small portion of the skull above the mPFC was removed, and the dura mater was slit to insert a multiple unit cluster recording electrode (NB Labs, Denison, TX model number 544-d70015). This electrode consists of eight Teflon coated 50 μm stainless steel wires attached to a female strip connector. The wires were cut to 8 mm to reach the appropriate depth of the mPFC. The tips of the exposed wires were dipped in a heated solvent of polyethylene glycol, which after drying holds the wire tips together but quickly dissolves after they are inserted into the brain. The coordinates for the insertion of the electrode, which was positioned in the right hemisphere of the prefrontal cortex, were $A = 6$–10 mm, $L = +0.50$ mm, $V = 4.0$–6.0 mm. Four jeweler's screws were inserted anteriorly and posteriorly to the electrode, which bonded to applied dental acrylic and held the connector to the