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Research report

Differential activation of accumbens shell and core dopamine by sucrose reinforcement with nose poking and with lever pressing

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HIGHLIGHTS

- Instrumental modus operandi and dopamine transmission in the accumbens shell and core.
- FR1 lever pressing for sucrose increased dialysate dopamine in both shell and core.
- FR1 and FR5 nose poking for sucrose increased dialysate dopamine only in the shell.
- Passive sucrose presentation increased dopamine in the shell and core.
- Activation of core dopamine is modulated in relation to its behavioural compatibility.

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ABSTRACT

In order to investigate the role of modus operandi in the changes of nucleus accumbens (NAc) dopamine (DA) transmission in sucrose reinforcement, extracellular DA was monitored by microdialysis in the NAc shell and core of rats trained on a fixed-ratio 1 schedule to respond for sucrose pellets by nose poking and lever pressing respectively. After training, rats were tested on three different sessions: sucrose reinforcement, extinction and passive sucrose presentation. In rats responding by nose poking dialysate DA increased in the shell but not in the core under reinforced as well as under extinction sessions. In contrast, in rats responding by lever pressing dialysate DA increased both in the accumbens shell and core under reinforced and extinction sessions. Response non-contingent sucrose presentation increased dialysate DA in the shell and core of rats trained to respond for sucrose by nose poking as well as in those trained by lever pressing. In rats trained to respond for sucrose by nose poking on a FR5 schedule dialysate DA also increased selectively in the NAc shell during reinforced responding and in both the shell and core under passive sucrose presentation. These findings, while provide an explanation for the discrepancies existing in the literature over the responsiveness of shell and core DA in rats responding for food, are consistent with the notion that NAc shell and core DA encode different aspects of reinforcement.

1. Introduction

The notion that links dopamine (DA) to reward stands as one of the most popular, yet most debated issues in neuroscience. Evidence for a role of DA in reward was initially provided, starting almost 40 years ago, by studies on intracranial self-stimulation (ICSS) and on the effect of lesions of DA neurons and pharmacological impairment of DA transmission [1–3]. This role of DA in ICSS was later extended to all rewards, conventional and pharmacological [4–6]. In vivo monitoring of the activity of DA neurons and of DA transmission by a variety of techniques (extracellular recording, microdialysis, voltammetry and Positron Emission Tomography) also showed that rewards and reward-conditioned stimuli activate mesolimbic DA transmission [7–12]. As a result of those studies, further hypotheses on the role of DA in behaviour were proposed (learning, incentive-motivational, activational/sensory-motor) [13–18].

Recently, new evidence for a role of DA in reward has been provided by optogenetic studies. Thus, selective light driven stimulation of mesolimbic DA neurons projecting to the nucleus accumbens (NAc) is capable of inducing place preference [19] and of

Abbreviations: DA, dopamine; NAc, nucleus accumbens; FR, fixed ratio; ICSS, intracranial self-stimulation.

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maintaining instrumental responding with characteristics superimposable to those of classical ICSS [20–22] in a DA D1 and D2 receptor dependent manner [23]. These observations provide compelling evidence that DA is linked to reward not only post hoc, as a consequence, but also *propter hoc*, as a cause [24]. Therefore, even in those conditions in which activation of NAc DA transmission is the consequence rather than the cause of reward, mesolimbic DA is likely to add a positive valence to the reward experience, over and above other functions (incentive, learning, value computation etc. etc.).

The NAc, however, is an heterogeneous structure, being made of two subdivisions, the shell and the core, with different and eventually opposite functions [9,11,25–28]. Microdialysis studies show that amphetamine- and cocaine-like psychostimulants increase extracellular DA preferentially or, depending on the dose, selectively in the NAc shell as compared to the core when administered response non-contingently [29–32] as well as contingently by i.v. self-administration [31,33]. Recently, we have shown that lentiviral-siRNA-induced silencing of D1 receptor expression in the NAc shell but not core prevents acquisition of cocaine self-administration [34]. Therefore NAc shell DA is necessary for cocaine reward.

On the other hand, in vivo microdialysis and voltammetric studies suggest that NAc shell DA encodes the hedonic valence of food taste. Thus, in naive rats, a salient sweet taste (chocolate) increases, while a bitter taste (quinine) decreases DA transmission in the NAc shell. This contrasts with the ability of both sweet and bitter tastes to increase dialysate DA in the NAc core and medial prefrontal cortex, in turn consistent with encoding of generic salience, rather than hedonic valence, by DA in these areas [35].

We have recently reported that in rats responding for sucrose pellets by nose poking, extracellular DA increases selectively in the NAc shell [36,37]. Our observations, however, contrast with those of the literature showing that in rats responding for food, extracellular DA increases both in the NAc shell and core [38–42]. As we have already noted [36], the most consistent difference between our studies and those of the literature is that they utilized lever-pressing instead of nose-poking as operant response. However, the existence of other experimental differences in the rewarding value of the reinforcer, degree of food deprivation, training procedure, operant schedule, etc., makes impossible to establish if indeed the differences in modus operandi were critical for the differences in the profile of the DA responses among shell and core [36,37].

In order to clarify this issue we compared the changes in extracellular DA in the NAc shell and core in two groups of rats differing only in the response modality utilized for responding, lever-pressing and, respectively, nose-poking for sucrose pellets on a FR1 schedule. In order to control for a role of effort and/or schedule ratio in performing the response we also ran in parallel a group of rats nose poking for sucrose pellets on a FR5 schedule.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Harlan Italy, Udine, Italy) weighing 250–275 g were housed in group of six per cage with standard food (MIL topi e ratti, GLP diets, Stefano Morini, S. Polo D'Enza, RE, Italy) and water ad libitum, for at least one week in the central animal room, under constant temperature (23 °C), humidity (60%) and a 12 h light/dark cycle (light from 8.00 a.m. to 8.00 p.m.).

All animal experiments were conducted in accordance with the guidelines for care and use of experimental animals of the European Communities Council (2010/63/UE L 276 20/10/2010) and with the Italian law (DL: 04.03.2014, N° 26) and approved by the Ethical Committee of University of Cagliari (CESA). All efforts have been made to minimize suffering and the numbers of animals used.

2.2. Surgery

Rats were anaesthetized with Equitesin (0.97 g pentobarbital, 4.25 g chloral hydrate, 2.1 g $MgSO_4$, 42.8 ml propylene glycol, 11.5 ml 90% ethanol/100 ml; 5 ml/kg i.p.). A guide cannula (Plasticone, Roanoke, VA, USA) (Ø: 0.022 mm) was stereotaxically and unilaterally implanted, randomly in the left or in the right hemisphere. Under the following coordinates: NAc shell (A: 2.0; L: 1 from bregma, V: −3.6 from dura), NAc core (A: 1.6; L: 1.9 from bregma, V: −3.4 from dura) according to the atlas of Paxinos and Watson. Guide cannulae were plugged with a dummy cannula.

After surgery, rats were housed in individual cages (45 cm × 21 cm × 24 cm) under the same conditions mentioned above. Rats were left to recover for 10 days and during the first 5 days they were administered with Gentamicin sulphate (40 mg/kg s.c.). Rats were manipulated once a day for 5 min during the whole training period.

After recovery rats were fed with 15 g of standard food each day (MIL topi e ratti, GLP diets, Stefano Morini, S. Polo D'Enza, RE, Italy) in order to keep their weight around 90% of their ad libitum weight. Water was available ad libitum for the whole duration of the experiments.

2.3. Microdialysis

2.3.1. Probe preparation

Microdialysis probes were prepared according to the method of Lecca et al. [43,44], using AN69 membrane (Hospal Dasco, Italy). The dialyzing portion of the probe was 1.5 mm long and the diameter of final probe was 310 μm. For each experimental session a new probe was utilized.

2.3.2. Microdialysis experiments

At the beginning of each microdialysis session, the microdialysis probes were connected to an infusion pump and perfused with a Ringer's solution (147 mM NaCl, 4 mM KCl, 2.2 mM $CaCl_2$; see Lecca et al. [44] on the use of 2.2 mM Ca^{2+} in the Ringer) at a constant rate of 1 μl/min, the dummy cannula was removed and the microdialysis probe was inserted through the guide cannula. The final coordinates of the microdialysis probe were: NAc shell (A: 2.0; L: 1 from bregma, V: −7.6 from dura), NAc core (A: 1.6; L: 1.9 from bregma, V: −7.4 from dura). Rats were placed in the operant box. After 10 min dialysate samples (5 μl) were started to be taken every 5 min [36,37] and injected without purification into a high-performance liquid chromatograph (HPLC) equipped with a reverse phase column (LC-18 DB, 15 cm, 5 μm particle size, Supelco) and a coulometric detector (ESA, Coulochem II, Bedford, MA) to quantify DA. The first electrode of the detector was set at +125 mV (oxidation) and the second at −175 mV (reduction). The composition of the mobile phase was: 50 mM NaH_2PO_4, 0.1 mM Na_2-EDTA, 0.5 mM n-octyl sodium sulfate, 15% (v/v) methanol, pH 5.5 (obtained adding Na_2HPO_4). With these conditions the sensitivity of the assay for DA was 5 fmol/sample. Basal dialysate DA was calculated as the mean of the last three consecutive samples differing by no more than 10%, collected during the 60-min period preceding each experimental session [36,37].

At the end of each microdialysis session the probe was removed and the guide cannula was plugged again with a sterilized dummy cannula. Each rat was then returned to the home cage.