Reward shifts and motor responses following microinjections of opiate-specific agonists into either the core or shell of the nucleus accumbens

Abstract Differences in pharmacology, anatomical connections, and receptor densities between the “core” and “shell” of the nucleus accumbens suggest that behavioral activity normally modulated by the accum- bens, such as reward and motor functions, may be differentially regulated across the mediolateral axis. This study investigated the effects of opiate receptor-specific agonists on reward and motor functions in either the accumbens core or shell, using the intracranial self-stimulation (ICSS) rate-frequency curve-shift method. Microinjections of the mu opiate receptor-specific agonist, DAMGO (vehicle, 0.03 nmol, and 0.3 nmol), or the delta opiate receptor-specific agonist DPDPE (vehicle, 0.3 nmol, 3.0 nmol), were administered bilaterally in a random dose order with a minimum of 3 days between injections. Rats were tested over three consecutive 20-min rate-frequency curves immediately following a microinjection to investigate the time course of drug effects. Both opiate agonists decreased the ICSS frequency necessary to maintain half-maximal response rates when injected into the medial and ventral shell region of the accumbens. However, DAMGO microinjections into the lateral accumbens core or the control site of the caudate increased the frequency necessary to elicit half-maximal response rates, while DPDPE microinjections into these regions had no effect. Evaluation of motor effects showed that administration of DAMGO resulted in a suppression of activity in all locations. In contrast, DPDPE microinjections resulted in little or no effect on lever pressing activity at any location.

Key words DAMGO • DPDPE • Mu • Delta • Opiate receptor • Intracranial self-stimulation • Reward

Introduction

Extensive research has been devoted to investigating the role of the nucleus accumbens (NAC) in both motor and reward functions. Pharmacological and anatomical findings over the past 2 decades indicate that the accumbens has at least two and as many as five discrete subdivisions (Záborszky et al. 1985; Groenewegen et al. 1987; Voorn et al. 1989; Zahm and Heimer 1990, 1993; Heimer et al. 1991; Berendse et al. 1992; Zahm and Brog 1992; Jongen-Rêlo et al. 1993). Immunohistochemical results show that two major subregions within the NAC are divided along the mediolateral axis. For example, the medial and ventral NAC regions, termed “shell” in the Paxinos and Watson (1986) atlas, show sparse immunoreactivity for calcium binding protein (CaBP) (Martin et al. 1991; Zahm and Brog 1992; Jongen-Rêlo et al. 1994), a low to moderate enkephalin (ENK) immunoreactivity (Herkenham et al. 1984; Voorn et al. 1989) and heavy immunoreactivity for substance P (SP; Zahm and Heimer 1988; Voorn et al. 1989; Zahm 1989; Zahm and Brog 1992); acetylcholinesterase (ACh-E; Herkenham et al. 1984; Záborszky et al. 1985), neurotensin (Heimer et al. 1991) and cholecystokinin (CCK; Záborszky et al. 1985; Heimer et al. 1991). In contrast, the dorsolateral NAC, termed “core” (Paxinos and Watson 1986), shows the opposite staining pattern, with heavy CaBP immunoreactivity, heavy to moderate ENK immunoreactivity, and sparse immunoreactivity for SP, ACh-E, neurotensin, and CCK (Herkenham et al. 1984; Záborszky et al. 1985; Zahm and Heimer 1988; Voorn et al. 1989; Heimer et al. 1991; Martin et al. 1991; Zahm and Brog 1992; Jongen-Rêlo et al. 1994). HPLC studies have also found differences between the core and shell subregions.
Deutche and Cameron (1992) showed that both DA and serotonin concentrations are higher in the shell than in the core.

Results from anatomical studies support the pharmacological subdivision of the NAC. Distinct afferent and efferent projections are segregated along the mediolateral axis in the caudal two-thirds of the NAC (Záborzszyk et al. 1985; Groenewegen et al. 1987; Witter et al. 1990; Zahm and Heimer 1990; Heimer et al. 1991; Berendse et al. 1992; Zahm and Brog 1992; Zahm and Heimer 1993). Receptor binding studies show a transition from low naloxone binding levels in the lateral NAC to moderate naloxone binding levels in the medial NAC (Herkenham et al. 1984). Mediolateral differences with delta opioid receptor densities have also been seen within the NAC. Dilts and Kalivas (1990) showed that the medial NAC contains the highest labeling of \textsuperscript{125}I-DPDPE and that this density diminishes laterally.

While there is general agreement that the NAC is involved in opiate-induced reward and motor functions, discrepancies within the literature exist. For example, some opiate reward studies have found that morphine administered into the NAC does not increase conditioned reward (Cunningham and Kelley 1992a,b), while 6-OHDA NAC lesions are ineffective in disrupting opiate self-administration (Dworkin et al. 1988). However, others have found rats will self-administer morphine directly into the NAC (Olds 1982) and that NAC morphine microinjections increase ICSS reward (West and Wise 1989), and produce place preference (Van der Kooy et al. 1982). Moreover, Smith et al. (1985) have shown that 6-OHDA NAC lesions disrupt opiate self-administration. These discrepancies may be due to differences of drug injection sites. For example, it is possible that those studies which produced no effects may have primarily manipulated the core regions, whereas studies detecting effects manipulated the shell. This study investigates the effects of delta and mu opiate-receptor activation on reward and motor functions in core and shell regions of the NAC. The intracranial self-stimulation method is used to test opiate effects because it separates reward from motor effects (for review see Stellar et al. 1988; Stellar and Rice 1989).

### Materials and methods

#### Subjects and surgery

Subjects were albino male rats ($n = 42$) (Charles River, CD strain) housed individually in standard plastic cages under 12:12-h reversed day-night cycle with free access to food and water. Rats were tested during their dark phase.

All rats were anaesthetized with pentobarbitul (60 mg/kg IP) after pretreatment with atropine (0.5 mg/kg SC). All rats were implanted with 23-gauge bilateral stainless steel chronic guide cannulae aimed at either the NAC core (AP: 2.2-0.7 mm from bregma; ML: $\pm 1.7$ mm from midline; DV: $-7.4$ mm from cortex; Paxinos and Watson 1986) shell (AP: 2.7-0.7 mm; ML: $\pm 0.9$ mm; DV: $-7.4$ mm) or the dorsomedial caudate (AP: 2.2-0.7 mm; ML: $\pm 1.4$ mm; DV: $-5.4$ mm), and a monopolar, flat-cut, 30 gauge, stainless steel electrode (Plastics One) aimed at the lateral hypothalamus (AP: $-3.0$ mm; ML: $1.7$ mm; DV: $-7.5$ mm). Cannulae were designed to allow 30-gauge injector tips to extend 3.0 mm beyond the outer cannulae. The electrode ground wire was attached to one of the four screws set in the skull and the assembly was secured with dental acrylic. When not receiving a drug infusion, the guide cannulae were fitted with wire stylets of equal length.

#### Drug injections

All drug injections were given immediately prior to the start of the 60 min session (three consecutive rate-frequency curves). Microinjections of DAMGO (0.0, 0.03 nmol = 0.015 μg, 0.3 nmol = 0.169 μg) or DPDPE (0.0, 0.3 nmol = 0.193 μg, 3.0 nmol = 1.93 μg) were bilaterally administered in a random dose order through the 23-gauge guide cannulae with 30-gauge injector tips in conscious, hand-held rats. All injector tips were coated with bovine serum albumin 5 min before infusion to inhibit drug adherence to the injector apparatus. Both DAMGO and DPDPE were dissolved in sterile 0.9% saline and delivered in a 0.5 μl total volume bilaterally over