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NEUROTOXIC LESIONS OF THE CAUDATE-PUTAMEN ON A REACHING FOR FOOD TASK IN THE RAT: ACUTE SENSORIMOTOR NEGLECT AND CHRONIC QUALITATIVE MOTOR IMPAIRMENT FOLLOW LATERAL LESIONS AND IMPROVED SUCCESS FOLLOWS MEDIAL LESIONS

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Abstract—Reaching for food, or skilled reaching, is used as a test of basal ganglia function in preclinical studies as well as studies of human neurological conditions. Although changes in the end-point measure of success document the effects of neurotoxic cellular damage to the caudate-putamen and its treatment in rodents, there has been no examination of the cause of change in success after neurotoxic lesions of the striatum. This objective was addressed in the present study, in which rats trained to reach for single food pellets with one forelimb, received contralateral quinolinic acid or ibotenic acid lesions of the medial and lateral caudate-putamen. Over 21 postsurgical days, reaching performance was scored for success and qualitative changes in movement elements were examined using frame-by-frame video analysis. In the acute postoperative period, extending over 3 to 4 days, the rats with lateral lesions transported their forelimb and grasped the food, but then ignored the food and did not withdraw their limb to their mouth. After recovery of the withdrawal movement, the rats displayed chronic qualitative impairments in the rotatory movements of aiming, pronating, and supinating the forepaw. Medial quinolinic lesions improved success relative to control rats and did not change qualitative aspects of limb movement. The acute dissociation between transport and withdrawal, the chronic qualitative changes in movement elements, and the differential effect of medial and lateral injury on success, support a complex contribution of the caudate-putamen to skilled reaching that includes sensorimotor neglect, and quantitative and qualitative motoric changes.

Key words: ibotenic acid and skilled reaching, medial caudate-putamen and reaching, neglect and caudate putamen, quinolinic acid and skilled reaching, striatum and skilled reaching, reaching withdrawal deficit.

Preclinical studies have been found to be useful in modeling anatomy, behavior, and the effects of injury to the basal ganglia of humans (Brown et al., 1997). Accordingly, reaching for food tasks (skilled reaching) in which an animal reaches for food with a forelimb that it then brings to its mouth for eating have been used to evaluate the effects of relatively cell-specific neurotoxic lesions to various regions of the caudate-putamen on skilled motor behavior (Aldridge et al., 1997; Bazzett et al., 1999; Block et al., 1993; Dobrossy and Dunnett, 2003; Dunnett et al., 1988; Evenden and Robbins, 1984; Fricker-Gates et al., 2003; Jeyasingham et al., 2001; Nakao and Brundin, 1997; Nakao et al., 1996; Pisa, 1988; Pisa and Cyr, 1990; Pisa and Schranz, 1988; Whishaw et al., 1986). These studies have documented impairments in food retrieval success, especially from lateral caudate-putamen injury, but the cause of the impairment in success has not been investigated. Extrapolations from a variety of lines of investigation suggests the caudate-putamen's contribution to this motor act may include learning (Block et al., 1993; Featherstone and McDonald, 2004; Fricker-Gates et al., 2003; Packard and Knowlton, 2002), attention (Aldridge et al., 1997; Karnath et al., 2002; Mittleman et al., 1988; VanVleet et al., 2002), spatial orientation (Brown et al., 1989), sensorimotor detection (Block et al., 1993; Connolly and Burns, 1993; Chudler et al., 1995; Groves, 1983; Jeyasingham et al., 2001), motivation (Cardinal et al., 2002), or movement selection (Redgrave et al., 1999). Because the caudate-putamen shares a number of connections with motor cortex (Alexander et al., 1986; Lapper and Bolam, 1992; Cheatwood et al., 2003, 2005; Connolly and Burns, 1993; Whetsell, 2002), it is also possible that impairments are motoric (Dobrossy and Dunnett, 2003). One of the difficulties in evaluating the cause of impairments in skilled reaching following caudate-putamen lesions is that end-point counts of success provide little insight into underlying causes of changes in success. The objective of the present study was to further examine the contribution of the caudate-putamen to skilled reaching by evaluating the qualitative changes in skilled reaching using slow motion video analysis methods.

The movements made by the rat when reaching for food are characteristic and distinctive and so their analysis can provide insights into the underlying cause of deficits in reaching success (Whishaw and Miklyaeva, 1996; Whishaw, 2005). Rats trained to reach through a slot for single food pellets from a shelf combine a number of separate actions to obtain food: (1) they locate and orient their body to the food using olfaction (Whishaw and Tomie, 1989), (2) they then transport a paw to the food to grasp it, and if the

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Abbreviations: ANOVA, analysis of variance; AP, anteroposterior; BDA, biotinylated dextran amine; DAB, 3,3′-diaminobenzidine; DV, dorsoventral; ML, mediolateral.

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grasp is successful, (3) they withdraw the food and bring it to the mouth. Orienting, limb transport for grasping, and limb withdrawal for eating are learned separately and sequentially, suggesting that skilled reaching is composed of a number of separate actions (Gharbawie and Whishaw, 2006). The actions of limb transport and limb withdrawal are also distinctive in that they consist of movements of the proximal limb in order to aim, pronate, and supinate the paw (Whishaw and Pellis, 1990; Hyland and Jordan, 1997) and the distal limb in order to orient, open, and extend and close the digits (Gharbawie et al., 2006). Motor system damage impairs the rotatory movements of the limb in both transport and withdrawal, but animals can reacquire successful reaching ability using compensatory movements of the body. For example, following motor cortex lesions, shifts in body weight and body rotation substitute for impairments in advancing the limb, pronating the paw to grasp food, and supinating the paw to place the food into the mouth (Whishaw et al., 1991; Whishaw, 2000). Because the movements used in skilled reaching are now well documented and can be evaluated using frame-by-frame video analysis, their quantification can aid in assessing the function of the caudate-putamen and the changes in success that result from its injury.

For the present study, rats were trained to reach for single food pellets that were placed on a shelf adjacent to a slit through which the animals could reach. Once trained, groups of animals then received neurotoxic unilateral lesions to the cells of lateral striatum with either quinolinic or ibotenic acid and to cells of the medial striatum using quinolinic acid. The neurotoxins extensively damage striatal neurons even though there are differences in neuronal populations most sensitive to each neurotoxin (Winn et al., 1991; Inglis et al., 1993; Inglis and Semba, 1997). Both prior to surgery and for an extended period postsurgery, the animals were video recorded during the skilled reaching tests so that their behavior could be subsequently analyzed using frame-by-frame scoring of the video record.

EXPERIMENTAL PROCEDURES

Animals

Forty-four male Long-Evans hooded rats, approximately 90 days old, weighing between 325 and 500 g, were used in the study. Rats were housed in Plexiglas cages with a bedding of sawdust in groups of two. The colony room was temperature and humidity controlled and had a 12-h light/dark cycle (08:00–20:00 h). Testing and feeding were done during the light portion of the cycle. Water was always available. The experiments were approved in relation to guidelines of the University of Lethbridge Animal Care committee as set out by the Canadian Council for Animal Care. All efforts were made to minimize the number of animals used and their suffering.

Feeding

Rats were fed approximately 20 g of Purina rat chow once a day in addition to the food pellets they obtained while reaching. Once testing began, food was given after the daily tests (Whishaw and Pellis, 1990). The weight of the rats was maintained at about 90–100% of their expected body weight. In the reaching test, the rats were reinforced with 45 mg dustless precision pellets (product F0021; Bioserve Inc., Frenchtown, NJ, USA).

Neurotoxins

Quinolinic acid. Quinolinic acid was dissolved in 0.1 M phosphate-buffered saline to a concentration of 30 mg/mL. The solution was then titrated to pH 7.4 with sodium hydroxide. Quinolinic acid was infused at a rate of 0.175 μL/min over a period of 1 min and 20 s per site, and was then left to diffuse for 2 min (Featherstone and McDonald, 2004).

Ibotenic acid. Ibotenic acid was dissolved in 0.1 M phosphate-buffered saline to a concentration of 9.49 mg/mL. The solution was then titrated to pH 7.4 with sodium hydroxide. Ibotenic acid was infused at a rate of 0.166 μL/min over a period of 1 min, and was then left to diffuse for 2 min (Whishaw et al., 1986).

Both quinolinic acid and ibotenic acid were delivered via a 30 gauge stainless steel cannula connected by polyethylene tubing to a 10 μL syringe mounted in a microdrive pump.

Surgery and group assignment

Animals assigned to control and lesion groups were matched on the basis of presurgical success scores. All rats were anesthetized with isoflurane gas, and following surgery received an analgesic (buprenorphine, 0.05 mg/kg, s.c.). Surgery was undertaken using standard stereotaxic procedures (Paxinos and Watson, 1982; Featherstone and McDonald, 2004).

Control. Eighteen rats served as the control group and were anesthetized and their skulls exposed and sutured but received no other surgery.

Medial caudate-putamen. Ten rats received medial caudate-putamen lesions and served as a lesion control group. They received injections of quinolinic acid using the following anterior and posterior coordinates in relation to bregma and the midsagittal suture, and the skull surface: anteroposterior (AP) +1.6, mediolateral (ML) ±−1.9, dorsoventral (DV) −5.8; AP +0.5, ML ±−2.2, DV −6.0; and AP −0.8, ML ±−2.8, DV −4.6.

Lateral caudate-putamen. Sixteen rats received lateral striatum lesions with quinolinic acid and eight rats received lateral striatum lesions with ibotenic acid. Coordinates of the three infusion sites were AP +1.6, ML ±−3.0, DV −6.2; AP +0.5, ML ±−3.7, DV −6.6; and AP −0.8, ML ±−4.5, DV −6.6.

Skilled reaching boxes

Animals were trained on a single pellet reaching task (Whishaw and Pellis, 1990). The boxes were made of clear Plexiglas with dimensions of 45×14×35 cm. In the center of the front wall was a vertical slit, 1 cm wide, and extended from 2 cm above the floor to a height of 15 cm. On the outside of the wall, in front of the slit, a 2 cm wide by 4 cm long shelf was mounted 3 cm above the floor. Two indentations on the surface of the shelf were located 2 cm from the inside of the wall and were aligned with the edges of the slit where rats could reach. For each rat, a pellet was placed in the indentation contralateral to the limb with which the rat preferred to reach. The lateral placement of the food pellet prevented the rats from using the tongue to lap the pellet, and because the rats pronate the paw medially to grasp, this placement prevented them from successfully using the non-preferred paw to grasp the food (Whishaw and Pellis, 1990).

Video recording and replay

Reaching performance was video recorded using a Sony Video 8 CCD VII portable camera (Sony, Tokyo, Japan), with a shutter speed of 1/1000 s (Gharbawie and Whishaw, 2006). A two-arm