Stereotactic Neurosurgical Technique and Electrophysiological Study in Ablating the Ventromedial Shell of the Nucleus Accumbens

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Key Words

Nucleus accumbens · Stereotaxy · Electrophysiological monitoring · Obsessive-compulsive psychiatric disorders

Abstract

Objective: To describe in as much detail as possible the method for ablating the ventromedial shell of the nucleus accumbens (NAc) and investigate the efficacy and safety of the ablation treatment. **Methods:** Sixty-five patients with drug addictions received operations within the time frame from 2004 to 2009. The ablation targets were located in the bilateral medial posterior inferior shell of the NAc. Intraoperative electrophysiological monitoring was performed. **Results:** Tissue impedance in the shell of the NAc varied from 185 to 355 Ω . When stimulated with a low frequency (2 Hz) and a voltage above 3 V, 57 out of 65 (87.7%) patients experienced slight throbbing sensations. During the lesion procedure, fever was detected on the head and face of 59 patients (90.8%), the heart rate decreased in 19 cases (29.2%), and restlessness, irritability and hyperalgesia were noted for all patients. Among the 65 patients, 52 (80%) no longer experienced a psychological craving for the drug. **Conclusions:** The shell of the NAc may be a promising surgical target for psychosurgery. Electrophysiological recordings revealed that the shell is indeed an appropriate structure.

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Introduction

The nucleus accumbens (NAc) is a poorly understood anatomical structure in the human brain. It is generally located dorsal to the caudal gyri of the orbitofrontal cortex and serves an essential role in motivational and emotional processes. Numerous studies pinpoint its involvement in some of the most disabling neurologic and psychiatric disorders, such as depression [1], schizophrenia [2], obsessive-compulsive disorder (OCD) [3], anxiety disorders [3], and drug abuse and addiction [4, 5]. The NAc is composed of distinct regions: the shell, which is confined to the ventromedial edge of the nucleus, and the core [6–8]. The shell of the nucleus is connected with the limbic system and the core with the extrapyramidal motor system [9–12]. Ablation of the NAc has been used historically to treat OCDs, anxiety disorders and epilepsy for over 10 years. Recently, studies have begun to identify benefits of ablating or stimulating the NAc for the treatment of heroin addiction [13–15]. The authors thought it plausible that ablating the NAc would reduce or remove the rewarding effects of heroin. Upon reviewing those reports, we noticed that they all focused on the core of the NAc, rather than the shell. In this study, we tried to ablate the ventromedial part of the shell of the NAc. The report describes in as much detail as possible how we went about localizing, stimulating, lesioning and collecting and ana-

lysing the electrophysiological data. Through our research, we aim to promote interest in further investigating this target for psychological operative treatments.

Patients and Methods

Clinical Data

During approximately 5 years (January 2004 to November 2009), 65 patients presenting with drug addiction, including 62 males and 3 females aged 18–39 years, underwent an operation with the purpose of ablating the NAc shell. All drug addicts (heroin 53, meperidine 8, and heroin plus phenamine or amphetroxyn and/or triazolam 4) were also long-term, heavy smokers, ranging in use from 4 to 27 years (average 15.2 years) and 15–60 cigarettes/day (average 28.3 cigarettes/day). All had been treated repeatedly in mandatory drug detoxification centres between 3 and 52 times (average 11.5 times). However, most relapsed immediately or within several weeks following discharge from the hospital and reportedly suffered intense psychological dependence and cravings for habit-forming drugs that lead to depression, sleep disturbance, bad temper, irritability and hypomnesia. Some patients still maintained a keen craving for the drug, though they were no longer able to experience feelings of euphoria from drug use. The study was conducted after passing the ethics committee of Nanfang Hospital and all patients signed the informed consent form before surgical intervention.

Inclusion Criteria and Preoperative Preparation

Subjects were chosen for our study group based on the following prerequisites. (1) The patients had undergone regular medical treatment more than 2 times and had failed to recover. (2) Routine preoperative examinations and neuropsychological tests indicated no surgical contraindications. (3) Patients requested the surgical treatment firmly and voluntarily and completely understood the possibility for surgical complications. The drug addicts were subjected to preoperative evaluations by a psychologist, and the operation was performed 5–7 days after the total elimination of symptoms of physiological dependence via combined therapy, including substitutes and decrements of methadone and transferring drug use to chlorazepin, diazepam, clonazepam or aloperridin.

Surgical Procedure

Local anaesthesia was induced. An MRI-compatible CRW stereotactic frame with localizing fiducials was attached to the patient's head with the base ring placed as parallel as possible to the anterior commissure-posterior commissure (AC-PC) plane. A 1.5-tesla MRI scanner (GE Sigma Horizon) was used to obtain sagittal T1-weighted spin-echo localizer scans to identify the anterior and posterior commissures. An axial three-dimensional fast gradient recalled echo study was then performed at a 1-mm slice thickness from the level of the middle cerebral peduncle to above the level of the corpus callosum, parallel to the AC-PC plane. The stereotactic coordinates for the bilateral target points were then calculated.

The NAc is better visualized as a structure distinct from the caudate and putamen (dorsal striatum) in its most posterior, ventral and medial portions, but its limits become more diffuse rostrally. This main (intermedio-posterior) portion of the NAc is eas-

ily delimited and measured by its stereotactic coordinates. However, it was not possible to distinguish the core from the shell of the NAc. Overall, there was no consistently distinct MR signal of the NAc comparative to the adjacent striatum (caudate, putamen), although in some slices, hypointensity of the NAc was detected in T1-weighted images.

The stereotactic coordinates of the NAc shell were determined based on its relativity to an orthogonal reference system including the midline and the AC-PC. The surgical targets were localized symmetrically in the bilateral ventromedial zones of the NAc posterior parts. The shape of the NAc shell was dorsally flattened similar to a human moustache, encircling the NAc core from the medial edge. The coordinates were calculated as 5.5 mm anterior to the AC, 5.0 mm lateral to the midline, and 6.0–8.0 mm below the AC-PC. The y-axis value was relatively invariable, requiring little adjustment. The x-axis value was regulated slightly based on the asymmetry of the width of the longitudinal fissure and the thickness of the cortical grey matter of the bilateral frontal lobe; the value was also set to maintain the distance between bilateral targets at 10–11 mm. The z-axis value was adjusted based on the macroelectrode penetration depth below the inferior wall of the frontal horn of the lateral ventricle and the intraoperative electrophysiological monitoring, usually necessitating a large-amplitude adjustment.

Two precoronal frontal burr holes were made symmetrically and sequentially under local anaesthesia. The burr hole was 2.5 cm lateral to the midline and 2 cm anterior to the coronal suture. The passageway of macroelectrode puncturing from the burr hole to the NAc shell target inevitably went through the frontal horn of the lateral ventricle. Attempts to avoid the passage through the ventricle, as some authors pursued, led to dramatically variable lesion shapes due to the anatomical shape of the NAc shell. When the macroelectrode is penetrating through the superior and then the inferior walls of the frontal ventricle, the breakthrough must be carefully realized (fig. 1). The position of the target along the z-axis should be at least 4 mm below the inferior wall of the frontal horn of the lateral ventricle.

Electrophysiological monitoring is critical for correcting and affirming the target position. We used the radiofrequency apparatus Radionics RFG-3CF and a radiofrequency macroelectrode with a naked part of 1.6×3.0 mm. Life indexes of patients were closely observed during the operation. In addition, neurological examination was performed repeatedly during surgery, and we also asked patients a uniform set of questions about their feelings. For example, pain was measured by recording pain scores, and with this scale we can judge and ask the patient whether pain has diminished, increased or stayed the same. Our team comprised specialists from many fields, including stereotactic and functional neurosurgery (K.Y., H.L., S.Q.), neuroelectrophysiology (K.W., B.X.), mental psychology (Y.Y.) and intensive care medicine (Y.S.).

Postoperative Follow-Up

A document of every discharged patient was established; we called them or visited them again (performed drug urinalysis) 3 months, half a year, 1 year, and once a year after being out of hospital. Therapeutic effect was divided into three grades, ranging from excellent (no relapse, psychological craving for the drug was eliminated), to good (occasional relapse, psychological craving for the drug was weakened to a degree that could be self-controlled) and to poor (relapse, psychological craving for the drug persisted to a strong degree).

Fig. 1. Simulated 3D images presenting the stereotactic coordinates of the lesioning electrode position. Green area = The cerebral ventricle; red area = the right NAc; brown area = the brain stem; yellow line = the passageway of macroelectrode puncturing from the burr hole to the right NAc shell target. Colors refer to the online version only.

Results

Detailed Steps

(1) The tissue impedance was recorded during the puncturing of the macroelectrode into the brain, and 230–350 Ω was attained upon arriving at the target area. Low impedance, below 180 Ω , indicated that the naked tip of the macroelectrode was near the inferior wall of the lateral ventricle and had not yet reached the condensed grey nucleus; as a result, the puncturing depth would be

adjusted to 4–8 mm below the inferior wall of the lateral ventricle. (2) At first, electrophysiological stimulating was conducted at a low frequency (2 Hz). When the stimulation voltage was less than 3 V, no abnormal feelings were induced. When the voltage surpassed 3 V, most patients complained of slight throbbing sensations at the nose tip and root and/or upper lip, showing no difference bilaterally. No visible muscle beating was observed. (3) When electrophysiological stimulation was performed at a high frequency (100 Hz) with a voltage around 1 V,

Fig. 2. Examples of postoperative MRI scans. Axial (a), coronal (b) and sagittal (c) images at 7 days. The arrows indicate the lesions in the NAc shell.

some of the patients began to complain of slight tingling and/or the sensation of an ant walking on the skin of the nose and lips, symmetrically distributed and without lateralization. When the voltage exceeded 2.5 V, all patients felt tingling and numbness across the whole area of the nose and mouth. When the stimulation voltage fell between 2 and 3.5 V, patients experienced calm moods, euphoria, hypoalgesia and light illusions, all of which were enhanced with voltage increase. Meanwhile, patients felt very cheerful and often requested for repeated and longer stimulation. This euphoria was similar to that induced by drug administration, with slight variations of degree. When electrophysiological monitoring and target ablation were performed from one side to the other, the reaction induced by the electrophysiological stimulus resulted in no difference in sequence between the left and right sides, but it was mitigated when the target of the opposite side was ablated. (4) During preliminary ablation under 45°C, patients had no complaints and presented no change in heart rate, breathing or blood pressure. No abnormal sensations were felt, and motion and pathological reflexes were normal. (5) Lesioning lasted 70 s at 75°C per site using the Radionics radiofrequency generator. A lesion of about 3 × 3 × 8 mm (fig. 2) was obtained. During the first lesioning, when the radiofrequency coagulation lasted 45–70 s, patients began to experience fever sensations on the head and face, followed by the neck. Even whole-body fever, accompanied by different degrees of diaphoresis, was sustained for about 30 s before gradually disappearing. The feeling of fever lessened greatly

during lesioning at the second site. After the ablation procedure was complete, several patients displayed decreased heart rates at 10–20 beats/min less than preoperation measurements. All patients displayed hyperalgesia, restlessness, irritation and even anger to certain degrees, and the emotional complaints lasted relatively long, for about 2 h to 3 days. Hyperalgesia, especially, appeared more frequently and lasted longer, and stable aches centred around the surgical incisions and screw fixations were common.

Electrophysiological Recording

In the suitable target, the shell of the NAc, tissue impedance was within the range of 185–355 Ω, with an average of $268.7 \pm 52.2 \Omega$.

When stimulated with a low frequency (2 Hz) and a voltage above 3 V, 57 patients (57/65, 87.7%) had slight throbbing sensations at the nose and upper lip. When stimulated with a high frequency (100 Hz), the threshold voltage at which the patients began to complain of slight tingling and/or the sensation of an ant walking on the skin of the nose and lips was $1.7 \pm 0.9 \text{ V}$, and the threshold voltage for inducing euphoria was $2.6 \pm 1.1 \text{ V}$.

During lesioning, 59 patients (59/65, 90.8%) exhibited a fever response on the head and face, heart rate decreased in 19 patients (19/65, 29.2%) and restlessness, irritability and hyperalgesia were present in all patients.

Short-Term Postoperative Response

Twelve patients complained of a brief decrease in heart rate, of whom 11 needed no special treatment, and the

response-related symptoms subsided within several minutes to 72 h. Only 1 patient complained of chest distress and weakness, which were relieved in 7 days with intermittent atropine treatment.

Intra- and postoperatively, 24 patients complained of aggravated restlessness and irritability, of whom 7 were prescribed sedatives due to severity, and the other 17 only needed observation. All recovered gradually within 3 days.

Pain concentrated at the surgical incision was a complaint of 48 patients, 41 of whom were prescribed analgesics. All were relieved of pain within 72 h. Five patients were found to be bulimic and were normalized within 1 week without any special therapy.

Effect on Drug Dependence

The mean follow-up period was 42 months (range 6–96 months). With long-term follow-up, the therapeutic effect was excellent in 52 patients (52/65, 80%). The drug-free time for these patients was more than 2 years in 37 cases (more than 4 years in 22 cases; the longest drug-free time was 8 years up till now), and less than 2 years but more than 1 year in 15 cases. The therapeutic effect was good in 7 (7/65, 10.8%) and poor in the remaining 6 patients (6/65, 9.2%), who maintained psychological dependence and relapsed 2 weeks to 6 months following the operation.

Effect on Tobacco Dependence

The 65 drug addicts were all heavy smokers, and most of them displayed a decreased craving for tobacco immediately after the operation, with some reporting a pronounced, unsavoury bitterness in response to smoking and some even refusing to smoke. During the follow-up period, 27 patients dismissed tobacco, and the other 38 smoked less than before the operation, reducing the average number of cigarettes per day from 28.3 to 15.1. Analysis revealed that the surgical treatment also showed a significant effect on tobacco dependence (χ^2 test, $p < 0.01$).

Postoperative Assessment of Mental Status, Depression and Anxiety

Only 22 drug addicts underwent evaluation of mental status, depression and anxiety state before the operation and 1–6 years after the operation, using the Mini-Mental State Examination, the Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety. The data are exhibited in table 1. Mini-Mental State Examination analysis showed that our surgery did not have an impact on mental status, while the Hamilton Rating Scale for

Table 1. Psychological scale (mean $\pm$ SD)

	MMSE	HAMD	HAMA
Before the operation	28.8 $\pm$ 0.8	42.4 $\pm$ 4.5	29.2 $\pm$ 3.9
After the operation	29.1 $\pm$ 0.7	12.7 $\pm$ 5.3	10.7 $\pm$ 4.3

MMSE = Mini-Mental State Examination; HAMD = Hamilton Rating Scale for Depression; HAMA = Hamilton Rating Scale for Anxiety.

Depression and the Hamilton Rating Scale for Anxiety data revealed that the operation improved the patients' personality characteristics, such as dysphoria, depression and motivation ($p < 0.01$).

Politeness, attention, social communication, careful listening and expression of friendly affection improved dramatically after the operation, although no quantitative data were collected for these factors.

Discussion

Obsessive-compulsive symptoms may be the most important characteristics in drug addicts with psychological dependence. The patient offends knowingly and even has stably intensive psychological cravings for the drug without any obvious euphoric effect from administration. The main manifestation is similar to typical OCD. Medication therapy for these abnormalities has a long-standing history, but the results have not been satisfactory until now [16]. Surgical methods such as stereotactic ablation [13] and deep brain stimulation [16, 17] are both still in the investigative phase but have shown reliable benefits in recent years. In the field of surgical treatment, however, neurosurgeons face many complex problems, one of the most serious of them being the possible complication of severely altering the patient's personality. In addition, there have been major concerns regarding the safety and efficacy of neurosurgical procedures used to treat addiction and OCD. It is also worrisome that the operation could induce irreversible damage to the control of food intake, sexual behaviour and other, more mundane daily pleasures. Neurosurgeons must therefore establish meticulous surgical methods for each unique psychosis group incorporating less invasion, smaller and more accurately targeted lesions, extremely low complication rates, and no obvious adverse effects on personality and cognition. Finding and investigating the best target is ultimately the major objective.

We applied stereotactic ablation to the NAc shell to treat drug addiction, OCD, and epilepsy between 2004 and 2009. According to our clinical exploration, we defined the ventromedial portion of the NAc shell as the optimum target for lesioning and achieved good results and no irreversible complications. The most inspiring result was that the operation caused practically no change to personality and sentiment. The surgical ablation of this miniscule target has not previously been reported; therefore, we here describe in detail the operation procedure, concentrating on the positioning method, electrophysiological recording, and intraoperative patients' reactions induced by different stimulation parameters. The authors intend to recommend this surgical method to neurosurgeons interested in psychosurgery to eventually provide benefit to more patients suffering from drug addiction and other psychologically compulsive diseases. Our emphasis here is to describe the intraoperative observation.

The NAc is the most prominent part of the ventral striatum, covering a large area from the rostral basal forebrain to the AC. Many authors have recently demonstrated the importance of this nucleus in neurologic and psychiatric disorders [18–21]. The NAc is involved in neural plasticity, especially in reward-motivated processes, ranging from addiction to memory. In most studies, the NAc is divided into two distinct parts, the shell and the core. Few studies [10, 11], however, have addressed the distinction between the shell and core regions in basic physiologic reactions. It is well accepted that information is transmitted mainly from the shell to the core [22, 23]. The shell of the NAc makes connections with the limbic system and the core with the extrapyramidal motor system [9–12]. Very little morphometric and electrophysiological information is available on the NAc, especially regarding the shell region, and furthermore, the published data are contradictory [24, 25].

Recently, some studies have identified benefits of neurosurgical interruption for intractable OCD by stereotactic bilateral thermocoagulation of the circuits that connect the NAc [26–28]. The same results were achieved with NAc deep brain stimulation in OCD and anxiety disorders [3]. In China, some authors reported that ablating the NAc could reduce the obvious rewarding effects of heroin, with results from basic and clinical research [13]. However, no clinical study has yet directed attention to the NAc shell specifically. We considered that ablation of different parts of the NAc, even the different parts of the shell, could achieve variable effects and result in distinctive complications.

Our study found that stimulating the ventromedial shell of the NAc indeed induced various reactions, and high-frequency stimulation could evoke abnormal feelings, euphoria and increased pain thresholds. Patients showed no abnormal reactions during test lesioning.

During lesioning, the patients gradually presented with responses such as fever, lowered heart rate and restlessness 45 s after coagulation. These symptoms subsided gradually, and patients recovered to normal states within 3 days, suggesting that these abnormal reactions were related to the conduction of heat in the target and surrounding tissues. Therefore, damaging only the ventromedial portion of the NAc shell is very safe with a low complication rate.

Several doctors had reported on operations involving NAc ablation and deep brain stimulation in the NAc for OCD and drug addiction [13, 26]. After reviewing these reports and analysing the target positions, by intraoperative coordinates and postoperative MRI, we found that their targets for ablation were all located in the core of the NAc or the lateral part of the shell. For this reason, we report data from electrophysiological monitoring and patients' responses that differ greatly from these studies, which induced lower heart rates and phrenitis, but no euphoria or abnormal feelings along the nose and lips. These results reveal that there are many differences in neural functions between the core, the lateral part of the shell and the ventromedial portion of the shell and imply that the ventromedial portion of the shell, which could induce euphoria, may be the best target for psychosurgical procedures.

Patient data from electrophysiological monitoring and intraoperative reactions preliminarily indicate that the ventromedial portion of the NAc shell plays an important role in adjusting emotion. Euphoria induced by high-frequency stimulation also implies that this small target may harbour critical components of the reward centre. Meanwhile, the intraoperative and postoperative observations confirm the safety of precisely ablating the ventromedial portion of the NAc shell, showing evident benefits. In brief, our observations preliminarily imply that the minimally invasive operation in the ventromedial portion of the NAc shell may be an ideal psychosurgical procedure, presenting good efficacy, safety, and a low complication rate.

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