Modulation of food intake following deep brain stimulation of the ventromedial hypothalamus in the vervet monkey

Laboratory investigation

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Object. Deep brain stimulation (DBS) has become an effective therapy for an increasing number of brain disorders. Recently demonstrated DBS of the posterior hypothalamus as a safe treatment for chronic intractable cluster headaches has drawn attention to this target, which is involved in the regulation of diverse autonomic functions and feeding behavior through complex integrative mechanisms. In this study, the authors assessed the feasibility of ventromedial hypothalamus (VMH) DBS in freely moving vervet monkeys to modulate food intake as a model for the potential treatment of eating disorders.

Methods. Deep brain stimulation electrodes were bilaterally implanted into the VMH of 2 adult male vervet monkeys by using the stereotactic techniques utilized in DBS in humans. Stimulators were implanted subcutaneously on the upper back, allowing ready access to program stimulation parameters while the animal remained conscious and freely moving. In anesthetized animals, intraoperatively and 6–10 weeks postsurgery, VMH DBS parameters were selected according to minimal cardiovascular and autonomic nervous system responses. Thereafter, conscious animals were subjected to 2 cycles of VMH DBS for periods of 8 and 3 days, and food intake and behavior were monitored. Animals were then killed for histological verification of probe placement.

Results. During VMH DBS, total food consumption increased. The 3-month bilateral implant of electrodes and subsequent periods of high-frequency VMH stimulation did not result in significant adverse behavioral effects.

Conclusions. This is the first study in which techniques of hypothalamic DBS in humans have been applied in freely moving nonhuman primates. Future studies can now be conducted to determine whether VMH DBS can change hypothalamic responsivity to endocrine signals associated with adiposity for long-term modulation of food intake.

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KEY WORDS • anorexia nervosa • feeding behavior • nonhuman primate • obesity

Since the early 1990s, high-frequency DBS has revolutionized neurosurgical approaches for the treatment of movement disorders, as evidenced by its success as an intervention of choice for drug-resistant PD.5,7,21,29,55 It is estimated that between 1996 and 2006 > 300,000 patients worldwide were treated with DBS of the STN for PD,7 the ventrointermedius of the thalamus for essential tremor, the globus pallidus internus for primary generalized dystonia, and the thalamic nuclei for Tourette syndrome.20

Deep brain stimulation applications also have been extended to the treatment of epilepsy, obsessive–compulsive disorder, and refractory depression and to the control of orthostatic hypotension in patients with chronic neuropathic pain.17,19,20,56

Recently, electrodes were implanted in the ventromedial posterior hypothalamus for long-term DBS treatment of intractable cluster headaches.14,32,43,48 The therapeutic approach was based solely on the adoption of DBS methods used successfully in the treatment of PD, with the assumption that high-frequency DBS would elicit similar inhibitory effects on hyperactive posterior hypothalamus functional activity.29 Deep brain stimulation of the posterior hypothalamus was not evaluated in animal models before its application in humans, although the effects of electrical stimulation of the hypothalamus had been explored in different animal species, predominantly in nonhuman primates.4,26,27,41–43,50,52 These experiments, as well as earlier

Abbreviations used in this paper: ANS = autonomic nervous system; CRW = Cosman-Roberts-Wells; DBS = deep brain stimulation; GFAP = glial fibrillary acidic protein; IPG = internal pulse generator; MR = magnetic resonance; OD = outer diameter; PBS = phosphate-buffered saline; PD = Parkinson disease; STN = subthalamic nucleus; VMH = ventromedial hypothalamus.
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studies in the 1950s and 1960s, were designed for the evaluation of behavioral responses (feeding or sexual response) and cardiovascular reactions to electrical stimulation of discrete hypothalamic areas. However, the experimental settings usually entailed a restrained monkey seated in a chair with head fixation for electrode insertion, and the immediate killing of the animal often followed stimulation. Only recently have researchers studied the stereotactic placement of permanent DBS leads in freely moving, unrestrained monkeys; such stereotactic placement methods had only been used in humans.\(^\text{13,25,39}\) A nonhuman primate model uniquely allows targeting and stimulation parameters to be evaluated and optimized before their application in humans.

We assumed that high-frequency DBS in the vervet monkey VMH with stimulation parameters comparable to those used in human STN DBS for neuronal inhibition would produce a similar effect. Namely, the outcome of high-frequency STN DBS resembles a physical lesion during the period of stimulation. In humans, a physical lesion in the VMH (for example, caused by a neoplasm) leads to “hypothalamic obesity.”\(^\text{33,34}\) Thus, we hypothesized that during on/off periods of high-frequency VMH DBS in the monkey, the “reversible lesion” would cause changes in feeding behavior. With that rationale, we evaluated the feasibility and safety of long-term bilateral VMH DBS in normal, freely moving vervet monkeys as a potential intervention for eating disorders in humans.\(^\text{78}\)

### Materials and Methods

#### Animal Population

Two adult (8 years old) male vervet monkeys (Chlorocebus aethiops), weighing 6.9 and 7.5 kg, were housed in individual cages for the duration of the study. Animal care was provided in accordance with the Guide for Care and Use of Laboratory Animals (National Institutes of Health Publication 86-5-23, Bethesda, MD), and all procedures were approved by the Chancellor’s Animal Research Committee at the University of California, Los Angeles.

#### Magnetic Resonance Imaging and Surgery for VMH DBS

Each animal was initially anesthetized using ketamine (10 mg/kg, intramuscularly) followed by the administration of atropine sulfate (0.04 mg/kg, intramuscularly), maintenance doses of anesthetics (ketamine 20 mg/kg/hr and midazolam 0.2–0.4 mg/kg/hr, via the saphenous vein), and intubation. Before the imaging studies, an MR imaging-compatible stereotactic frame\(^\text{12,22}\) was secured with 4 pins to the animal’s zygomatic and occipital bones after local lidocaine injection. The stereotactic frame was designed to precisely fit the commercially available human stereotactic device CRW (Radionics, Inc.). A Radionics MRIA-LF locator (9 axial fiducial markers) was attached to the frame before the MR imaging (1.5 T; 3D spoiled gradient T1-weighted imaging; TR 35 msec, TE 9 msec, field of view 28 × 28 cm, matrix size 256 × 256; Siemens Symphony). Coronal, axial, and sagittal sections (1.0-mm slice thickness) were obtained throughout the striatum and midbrain.

#### Target Determination

The VMH targets were identified in a vervet brain atlas (http://labs.pharmacology.ucla.edu/mellab/vervet_atlas/) and a published stereotactic brain atlas of the same species\(^\text{18}\) in the planning stages and on MR imaging prior to surgery. Our atlas consists of scanned consecutive 1-mm-thick sections throughout the entire vervet brain and is stereotactically coded. The VMH target was identified on a coronal section at +6.44 mm anterior to the reference (0.00 mm) coronal plane and at A12 in the atlas of Contreras et al.\(^\text{10}\) (Fig. 1 upper left). Based on these reference images, the VMH was localized on the MR image 4 mm posterior to the full profile of the anterior commissure (or 6 mm posterior from the first rostral appearance of the anterior commissure), 2 mm lateral to the midline, and 2 mm superior to the ventral tip of the rostral portion of the nucleus corporis mammillaris. The stereotactic coordinates of each VMH target were then determined using a computer algorithm (BrainLAB@Target software, BrainLAB). On planning the entry points on the skull, trajectories, angles of entrance, and lengths from the surface of the skull to the target for the bilateral implantation of DBS electrodes, the coordinates and angles were dialed in the CRW arc-centered system and verified in a stereotactic phantom before surgery and electrode placement.

#### Electrode Implantation

Following MR imaging, the animal was transferred to the surgical suite and isoflurane (1–2%) was administered. Body temperature, oxygen saturation, pCO\(_2\), arterial blood pressure, and cardiac rate were continuously monitored electrocardiographically throughout the surgery by using an indwelling arterial catheter. The CRW human stereotactic device was attached to the frame affixed to the animal’s head for subsequent stereotactic surgical manipulations. After making a midline incision, the skull was accessed bilaterally and 1.5-mm-diameter holes were drilled for the approach to the hypothalamic target. A polyimide guide tube (OD 1.04 mm, inner diameter 0.89 mm; Phelps Dodge High Performance Conductors) fitted with a stainless steel stylet was stereotactically inserted into the brain bilaterally by using a micromanipulator. The distal tip of the guide tube was 4 mm above the VMH target. Three anchoring titanium screws (OD 1 mm, length 3 mm) were placed around the bur hole, and the guide tube was secured to the skull with acrylic cement. The stylet was removed, and the stimulating 4-polar DBS lead was stereotactically inserted through the guide tube using the micromanipulator. The distal tip of the inserted electrode protruded 4–5 mm from the tip of the guide tube. A miniature DBS lead (OD 0.635 mm, total length 15 cm; NuMED, Inc.) had at its distal end 4 90° platinum/10% iridium contacts, 0.5 mm long and spaced 0.5 mm apart. At the proximal end, the metallic contacts fit into a Medtronic Extension #7495 that was connected to the IPG (Itrel II 7424, Medtronic, Inc.). The lead was secured to the skull with acrylic and medical-grade silicone cements. The lead on each side was connected to the extension cord tunneled subcutaneously to the back of the animal. Left and right IPGs were subcutaneously implanted ~5–7 cm below each scapula, allowing unrestricted and free movement of the animal. Nonabsorbable sutures were used to secure the extension leads and IPGs.

#### Intraoperative Electrophysiology

Before connecting the leads to the IPG, intraoperative electrical stimulation was conducted in the monopolar mode, with the ground at the border of the scalp incision. A series of 1-minute continuous stimulations (1–3 V, 90 μsec, 185 Hz) for each of the 4 contacts was performed to detect any induction of ANS activity. Cardiac rate, arterial blood pressure, and pupillary status were recorded. Before surgery and for 6 days thereafter, the animal was given an antibiotic (Baytril 40 mg/day, intramuscularly); for 3 days after surgery, the animal received an analgesic (Buprenex 0.015 mg/kg, intramuscularly, twice a day).

#### Postoperative Electrophysiological Testing and DBS Programming

At 6–10 weeks after the surgical procedure, the animals were briefly anesthetized with ketamine (10 mg/kg, intramuscularly), intubated, and isoflurane (1.0–1.5%) was administered. Heart rate and arterial blood pressure were monitored during a series of on/off DBS periods of variable duration (1–5 minutes), depending on the reactions of the vital functions. All contacts (0–3) on both electrodes were tested with monopolar stimulation (1–3.5 V, 90 μsec, 185 Hz). The contacts and stimulation parameters that evoked minimal ANS activity were used for programming IPGs in the subsequent DBS experiments.

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Feeding Regimen and DBS

Animals were provided a standard monkey diet (PMI Nutrition International, Inc.), 16 biscuits/day (130 g) containing 15% protein, 5% fat, 6% fiber and daily rations of fruits, vegetables, and vitamins. The amount of biscuits consumed daily was recorded. Following an 8-day baseline period with DBS off, the animals received bilateral DBS (2.5 V, 90 μsec, 185 Hz). The IPGs were activated and inactivated transdermally on the animal’s back by a magnet after temporarily restraining it to a corner of the cage. An 8-day stimulation period (DBS on) was followed by a 2-day rest period (DBS off), a 3-day DBS-on period (3.5 V, 90 μsec, 185 Hz), and a 3-day DBS-off period before killing the animals.

Histological and Immunohistochemical Analysis

Animals were initially anesthetized with ketamine (10 mg/kg, intramuscularly) followed by heparin sodium (2000 U, intravenously) and then deeply anesthetized with pentobarbital (100 mg/kg, intravenously). They were transcardially perfused according to the modified fast perfusion protocol. Briefly, 0.5 L ice-cold 1% paraformaldehyde in 0.1 M PBS (pH 7.4) and heparin sodium (1000 U/L) were initially perfused over 1 minute. Then, 4 L ice-cold 4% paraformaldehyde in PBS was perfused over 12–15 minutes. Following its removal from the skull, the brain was cut coronally in 0.5-cm-thick blocks. These blocks were postfixed in 4% paraformaldehyde and 0.1% glutaraldehyde in PBS for 24 hours at 4°C and then cryoprotected by successive immersions in 10, 20, and 30% sucrose/PBS solutions.

Histochemical and immunohistochemical analyses were performed on cryostat-cut coronal sections (30 μm) from the precommissural and postcommissural brain blocks that encompassed the entire hypothalamic region. Every 20th section was stained with cresyl violet for anatomical identification. Contiguous sections were immunostained for GFAP, as previously described.

Statistical Analysis

Food intake data were analyzed using the Student two-tailed t-test, with statistical significance set at a probability level < 0.05.
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Results

Surgical Procedure

The surgical procedure was well tolerated without negative incident by both animals. On recovery from the anesthesia, they were able to perform self-maintenance in their home cages. No overt behavioral changes due to the surgical procedures were observed. Wound healing was uneventful except for the postoperative development of a seroma around the implanted IPG on 1 side of 1 animal’s back, which resolved after several days of antibiotic treatment.

Intraoperative and Postoperative DBS Testing

Results from the intraoperative and postoperative DBS applied while the animals were in a state of anesthesia were used as guidelines for determining the stimulation parameters and contacts that could be safely used in the DBS-on periods when they were conscious and freely moving. It was established that the most dorsal contacts, 2 and 3, bilaterally, when stimulated with amplitudes of 1–3.5 V, effected increases in heart rate and blood pressure 4–23% and 10–72%, respectively, above baseline values. In contrast, stimulation of the ventral contacts, 0 and 1, did not elicit a significant response in cardiovascular functions (< 2% above baseline values). The cardiovascular response was amplitude (voltage) dependent. Thus, stimulation of Contacts 2 and 3 with 2 V caused a 2–4% increase in the heart rate, whereas 3 V caused a 13–23% increase above baseline. During intraoperative DBS testing while the vervets were in a state of complete anesthesia (2% isoflurane), it was noted that the stimulation of all contacts with an amplitude of 3 V caused a 50% increase in pupillary diameter compared with the nonstimulated state in the eye ipsilateral to the site of DBS. The mydriasis ended when stimulation was turned off. Mydriasis was not observed during postoperative testing or during DBS in the conscious animals. Based on the above results, Contacts 0 (left side) and 1 (right side) and monopolar stimulation of 2.5–3.5 V, 90 μsec, and 185 Hz were selected for the subsequent studies.

Behavioral Observations

At the initiation of both DBS-on periods, the animals became acutely agitated. Over a period of 30 minutes, they defecated and urinated, had an erection, and repeatedly masturbated. These behaviors then subsided and were not observed during the remainder of the 8- or 3-day stimulation periods.

During the daily 30-minute morning and afternoon observations, 8 hours apart, aggressive behaviors (increases in head jerk threats, displays, yawns, rattling the cage, or reaching to the observer) were not observed during either the DBS-on or DBS-off condition.

Feeding Observations

Throughout this 4-month study (1-month quarantine pre-surgery, 2-month recovery postimplantation, 3-week DBS off/on regimen), there were no significant changes in body weight in either animal. For both DBS-on periods, food consumption increased, compared with levels during the DBS-off periods (Fig. 2).

Histological and Immunohistochemical Analyses

Accurate placement of electrodes in the VMH was established through histological analyses, with the dorsal electrode contacts extending into the dorsomedial nucleus and the ventral tip of the stimulating leads being positioned in the ventromedial region (Fig. 1 lower left and right). Postmortem histochemical and immunohistochemical analyses of the animals’ brains confirmed targeting accuracy in the VMH. Immunoreactivities to GFAP in the targeted area and along the electrode track were not qualitatively different from the surrounding tissues, indicating the absence of significant gliosis, an observation similar to that after long-term DBS implants in the human brain.

Discussion

Methodological Considerations

The accurate targeting of the vervet ventromedial hypothalamic region in this study has confirmed the utility of our previous use of human stereotactic methodology in nonhuman primate research. Our methods included the use of customized miniaturized leads to accommodate the smaller VMH target (rostrocaudal extent of ~ 3 mm and ventrodorsal extent of ~ 1.5 mm) within an average total vervet brain volume of 85–110 ml, relative to the 1500 ml of the human brain; the diameter of the applied electrode (0.655 mm) was half, and the stimulating contact’s length (0.5 mm) was one third of the standard dimensions used in the human. The external magnet activation of IPGs in the conscious and freely moving animals allowed ready access for initiating and terminating DBS periods. Recently, analogous preclinical studies in nonhuman primates have been successfully focused on the evaluation of DBS of the pedunculopontine nucleus in a normal and a parkinsonian monkey before applying the therapy in humans. In future studies, we will establish the long-term safety and efficacy of VMH DBS prior to consideration of potential human applications.

Stimulation Parameters and ANS Responses

Critical variables for DBS applications are the stimulation parameters, which in our study were selected from current human DBS protocols for various movement disorders and from our clinical experience. Based on that range of applications (Table 1), we verified, both intraoperatively and postoperatively, that our selected parameters in the targeted VMH region did not induce cardiovascular responses detrimental to the well-being of the animals. On electrical stimulation of the hypothalamus in humans, nonhuman primates, and rodents, increases in blood pressure and tachycardia have been ascribed primarily to sympathetic activation of the lateral hypothalamic area and neurons located in the perifornical area. However, as has been observed in baboons and in the present study, a cardiovascular response could be elicited by the stimulation of the dorsal VMH. To advance VMH DBS for human applications, the extent of sympathetic nervous system effects will likely be a function of electrode placement and the contact used for stimulation, given that the relatively large sizes of the electrodes/contacts preclude targeting of specific nuclei with the precision of electrophysiological studies.
Additionally, the creation of acute cystic cavities during the insertion of stimulating electrodes might explain these effects\(^5\) given that the traumatic cystic cavities increase the radial extension and significantly change the shape of the electrical field. For our study, the postmortem histological results did not show a cystic space or cavitations along the electrode track, probably accounting for the absence of mydriasis and ocular movements when the animals were stimulated 4–6 weeks postimplantation.

In addition to the postsurgical cardiovascular and ocular responses, both animals had brief periods of genitourinary stimulation on initiation of the 8- and 3-day DBS-on periods at 1 month after surgery. Previously, electrical stimulations of the medial preoptic area, lateral hypothalamus, and dorsomedial nucleus of the hypothalamus have all been shown to produce sexual behavioral responses in male non-human primates.\(^5\)–\(^8\) Thus, perhaps the DBS parameters resulted in some activation of neuronal firing, rather than the presumed inhibition associated with typical DBS procedures. That possibility can be explored in studies in which different activation parameters are systemically evaluated. The characterization of a voltage dependency for either the activation or inhibition of different ANS responses could then provide a rationale for the application of DBS in treating specific autonomic disorders.

### Modulation of Food Intake

Hypothalamus lesioning studies have been conducted in a range of animal species. Early experiments in monkeys\(^3\),\(^8\),\(^22\) showed that hyperphagia could be induced by electrolytic lesions in the VMH and that complete aphagia was produced when the lateral and middle parts of the anterior hypothalamus were destroyed.\(^3\) Yet, electrical stimulation of the VMH in restrained monkeys, usually seated in a primate chair, gave conflicting results, depending on the stimulation parameters and the exact site of stimulation. For example, VMH stimulation with a high current up to 1.0 mA (monophasic 1.0-msec pulse, 50 Hz) induced increased food intake,\(^41\) the effect being similar to that of the electrolytic lesion. Note, however, that when a lower current of \(\leq 100\ \mu A\) (0.2 msec, 50 Hz) was used, electrical stimulation of the VMH and the lateral hypothalamic area elicited suppression of bar-press feeding in hungry animals.\(^4\),\(^27\),\(^55\) whereas stimulation of the far lateral and ventral hypothalamic areas induced feeding in satiated animals. Furthermore, in food-deprived dogs, VMH stimulation (3.3 V, 100 \(\mu A\), 1.0 msec, 50 Hz) delayed their next food intake for 1–18 hours.\(^4\) Based on these early studies, the VMH was designated as the brain’s “satiety center”\(^7,28\) and the lateral hypothalamus as an “appetite center.” Note, however, that this dual concept of appetite regulation has been replaced by more integrated models of specific hypothalamic cell populations and their neural networks coupled to endocrine signals associated with adiposity\(^20\),\(^26\) and the regulation of energy expenditure.

Interestingly, in patients with PD treated with STN DBS, weight gain has been observed in the period of 1–45 months after the start of stimulation.\(^40\) Authors have hypothesized that the weight gain was consequent to the direct influence of STN DBS on the function of the lateral hypothalamus.

In our experiments with stimulation parameters similar to those used for STN DBS (Table 1), high-frequency DBS (185 Hz) of the VMH in the normal vervet monkey induced a moderate increase in food consumption. These results suggest that the stimulation parameters effected feeding pattern changes resembling those seen in the context of a partial and reversible VMH lesion, as evidenced by different amounts of food consumed in DBS off/on periods. For this study, however, we did not explore a range of electrical stimulation parameters that may have resulted in qualitatively and quantitatively different feeding behaviors. The high-frequency VMH DBS that was delivered continuous-
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TABLE 1
Deep brain stimulation parameters*

<table>
<thead>
<tr>
<th>Condition &amp; Treatment</th>
<th>Voltage (V)</th>
<th>Pulse Width (usec)</th>
<th>Frequency (Hz)</th>
<th>Relevant Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>human PD, STN DBS</td>
<td>1–3.5</td>
<td>60–210</td>
<td>130–185</td>
<td>Kancel &amp; Grill, 2004</td>
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<tr>
<td>human ICHs, hypothalamus, DBS</td>
<td>1–3.3</td>
<td>60–90</td>
<td>180–185</td>
<td>McIntyre et al., 2004</td>
</tr>
<tr>
<td>human impulsive/violent behavior, PMH DBS</td>
<td>1</td>
<td>60</td>
<td>185</td>
<td>Benabid et al., 2005</td>
</tr>
<tr>
<td>vervet monkey food intake, VMH DBS</td>
<td>2.5–3.5</td>
<td>90</td>
<td>185</td>
<td>Rodriguez-Oroz et al., 2005</td>
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<td>Schoenen et al., 2005</td>
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<td>Franzini et al., 2005</td>
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* ICH = intractable cluster headache; PMH = posteromedial hypothalamus.

ly for 8- and 3-day periods did result in statistically significant increases in food consumption, but these increases were not of a magnitude or duration that produced weight changes. Rigorous measurement of energy input–output balances and metabolism parameters was not part of this feasibility study. These variables are more appropriate for long-term DBS assessments because the adaptation and recruitment of neural networks in the vicinity of stimulating electrodes may be time dependent. For example, DBS lasting over months may be required for optimum results, as has been observed in the DBS treatment of dystonia that increasingly improved over 2 years.11

Presently, the surgical targeting of discrete nuclei within the hypothalamus does not represent a viable option for clinical interventions. However, the range and reversibility of DBS parameters allow targeting of hypothalamic subregions (for example, arcuate nucleus, paraventricular nucleus, lateral hypothalamic nuclei) to potentially reduce, block, or enhance their sensitivity to endocrine signals associated with food intake, satiety, and adiposity. Our nonhuman primate model represents a clinically applicable system for future comprehensive long-term VMH DBS studies that include monitoring of endocrine function and assessment of the metabolic rate, with the objective of advancing the application of DBS to humans.

Conclusions

Recently demonstrated DBS of the posterior hypothalamus as a safe and effective treatment for chronic intractable cluster headaches in humans has prompted this investigation of new venues for DBS. We are the first to apply human hypothalamic DBS methodology for modulating feeding behavior in a freely moving nonhuman primate. Stereotactic techniques used for human DBS were accurate and fully applicable to the much smaller brain of the vervet monkey. The bilateral electrode implants and stimulation of the VMH had no apparent adverse effects on the well-being of the animals. On stimulation, an initial period of sexual behaviors was observed. During periods of VMH DBS, total food consumption increased. These results have shown that VMH DBS represents a novel intervention strategy for producing reversible changes in feeding behavior.

References


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