The Role of NMDA Receptors in Human Eating Behavior: Evidence From a Case of Anti-NMDA Receptor Encephalitis

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Abstract: Research in animal models has implicated N-methyl-D-aspartate (NMDA) receptors (NMDARs) in the control of food intake. Until now, these findings have been not replicated in humans. Here we describe a 22-year-old woman with anti-NMDAR encephalitis and no prior neurological or psychiatric history. Her clinical course was marked by successive eating disorders: anorexia followed by hyperphagia. We propose that, much as they do in other animals, NMDARs in humans interact with the neuroendocrine, homeostatic, and reward systems controlling food intake in the central and peripheral nervous system structures related to feeding and satiety.

Key Words: N-methyl-D-aspartate, anti-NMDA receptor encephalitis, eating behavior, anorexia, hyperphagia

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G lutamate is the most abundant excitatory neurotransmitter in the central nervous system. The N-methyl-D-aspartate (NMDA) receptors (NMDARs) are glutamate-gated calcium channels that are important for synaptic plasticity processes like long-term potentiation.[1] NMDAR activation requires the binding of 2 molecules of glycine in the 2 NMDA Receptor 1 (NR1) subunits of the receptor, and 2 molecules of glutamate in the 2 NR2 subunits.[1] Since the mid-1990s several researchers have proposed that NMDARs play a role in the control of food intake in rats.[2–4] These studies strongly support NMDA stimulating a rat's feeding, mediated mainly by NMDAR agonism[5,6]; however, an NMDAR antagonist produces either an increase[7] or a decrease[8] in a rat's feeding, depending on the site where the antagonist is injected.

Anti-NMDAR encephalitis is a recently described autoimmune encephalitis of humans[9] in which antibodies target the NR1 subunits of NMDAR, leading to an internalization of surface NMDAR and causing a selective and reversible decrease in NMDAR surface density and function.[10] The condition causes neuropsychiatric symptoms like insomnia, memory deficits, and grandiose delusions, and neurological manifestations like abnormal choreoathetotic movements, seizures, dysautonomia, and coma. Patients can be of any age; most are female. The characteristic patient is a young woman with an ovarian teratoma, although not all patients have a tumor. In most patients, anti-NMDAR antibodies can be detected in the cerebrospinal fluid. Treatment involves removal of any tumors and first-line and second-line immunotherapy. An estimated 75% of patients with anti-NMDAR encephalitis recover completely or with mild sequelae; the other 25% remain severely disabled or die.[11]

We describe a young woman with anti-NMDAR encephalitis associated with successive eating disorders: anorexia followed by hyperphagia. This case supports the role of NMDA transmission in the control of food intake in humans.

CASE REPORT

A previously healthy 22-year-old woman with no neurological or psychiatric history presented to our hospital with spatiotemporal disorganization, confusion, and generalized epileptic seizures progressing rapidly to coma (Glasgow Coma Scale between 3 and 7). The cerebrospinal fluid showed 134×10^6/L white blood cells, and protein at 370 mg/L. The seizures required triple anti-epileptic therapy with clonazepam, levetiracetam, and valproic acid. We started empirical treatment with acyclovir, amoxicillin, and ceftriaxone. Two days later, we found anti-NMDAR antibodies in the patient's serum and cerebrospinal fluid. We did not find ovarian teratomas or other tumors. With the diagnosis of anti-NMDAR encephalitis, we changed the patient's treatment to prednisone 30 mg/day, 5 plasma exchanges, and 4 cycles of intravenous immunoglobulins, followed by azathioprine.
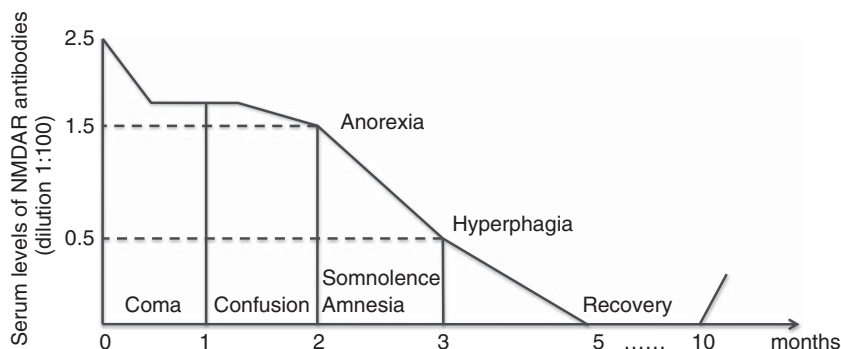
Figure 1 illustrates the patient's clinical course over the next 10 months. She stayed in a coma for the first month. Then her vigilance gradually began to improve. She responded to simple orders, but stayed confused, agitated, and disoriented to time and space. The fluid-attenuated inversion recovery sequence of a brain

FIGURE 1. Clinical course of our patient with anti-NMDAR encephalitis, showing her biphasic eating disorders. NMDAR indicates *N*-methyl-D-aspartate receptor.

magnetic resonance imaging scan revealed a discrete hypersignal in the frontotemporal cortex and in the hippocampal regions bilaterally.

Two months after her symptoms began, the patient had severe anterograde amnesia, dysautonomia, and alternations between irritability and somnolence. She was sleeping for longer than 15 hours/day. For the next month, the patient—who had been on prednisone (30 mg/day) since her diagnosis—refused to eat, and spat out every food that she was fed. She complained of dysgeusia, saying that food tasted like "stool." She also expressed a fear of gaining weight, and often talked about calories and fat content. She required parenteral nutrition for the month. During that time, we lowered her prednisone dose to 25 mg/day.

Then she gradually began to eat. After 2 days of eating, she entered a hyperphagic phase. She began eating hypercaloric foods, decreased her locomotor activity, and demanded double or triple the quantities of a normal meal. She even tried to eat from other patients' plates. Her premorbid body mass index had been 21 (normal); 4 months later it was 27 (overweight) and, 5 months after that, 31 (obese class I), even with nutritional consultation and her own efforts to restrain her eating.

Five months after her symptoms began, the patient had improved enough to be discharged home. She no longer had antibodies in her serum or cerebrospinal fluid, her dysautonomia and amnesia had regressed, and her hyperphagia had eased. She could perform her everyday activities independently. However, 5 months later (ie, 10 months after diagnosis), she again showed NMDAR antibodies. Imaging revealed bilateral ovarian teratomas, with no signs of malignancy. She underwent a bilateral ovarian cystectomy.

This woman had no history of anorexia or hyperphagia before her encephalitis. Moreover, no family history put her at high risk for an eating disorder, and no detectable external factor was causing her emotional distress or otherwise increasing her susceptibility to an eating disorder. She had no underlying bipolar mood disorder accompanying the changes in her eating habits, and she was not taking antidepressant medication.

DISCUSSION

Our patient presented with anti-NMDAR encephalitis that followed a classic course,[11] with marked improvement after 3 months. The most noteworthy of her neuropsychiatric manifestations was the sudden onset and succession of 2 eating disorders. The severity and compulsive character of her anorexic and hyperphagic episodes, both of which occurred while she was taking prednisone, do not seem to be related to the drug. Actually, her prednisone dose had already been decreased from 30 to 25 mg/day before she switched from anorexia to hyperphagia. Besides, compulsive hyperphagia—but not anorexia—has already been described in some patients as a symptom of anti-NMDAR encephalitis.[11] In the absence of a prior history of an eating or mood disorder, our patient's eating behavior was likely related to her encephalitis.

In line with robust evidence from animal studies, this case is consistent with a framework implicating NMDA transmission in the control of food intake in humans. This framework includes at least 3 types of involvement: neuroendocrine/homeostatic, hedonic/motivational, and anatomical.

NMDARs Interact With the Neuroendocrine/Homeostatic Mechanisms of Eating Behavior

Three of the most important biological factors controlling food intake in both animals and people are the neuropeptide Y (NPY), leptin, and hypocretin/orexin. In rats, it has been proposed that NPY increases appetitive ingestive behavior (searching for and approaching food), but inhibits consummatory ingestive behavior (chewing and swallowing) when food is available.[12] In humans, NPY is elevated in anorexic patients,[13] and it is thought to contribute to behavioral conditioning in situations in which reduced food intake was at first rewarding.[14] Leptin seems to have the opposite effects, inhibiting appetitive ingestive behavior[12] and decreasing NPY expression.[15] The hypocretin/orexin neurons of the lateral hypothalamus also play a role in eating behavior. Central administration of orexin A leads to increases in appetite, meal frequency, and length of meals[16] through

interactions with the NPY,[17] leptin,[18] and dopaminergic cell bodies of the ventral tegmental area (VTA).[19]

Several studies have shown that NMDA transmission interacts with leptin, hypocretin/orexin, and NPY signaling. Leptin is a binding partner for the NR1 subunit of NMDA, and enhances NMDA transmission.[20–22] Moreover, the control of feeding by hypocretin/orexin seems to depend on NMDARs, as antagonism of these receptors with concomitant orexin administration has led rats to eat less.[23] In contrast, NR1 antagonism by 7-chlorokynurenic acid has been shown to suppress NPY activity.[8] Interestingly, our patient's decrease in locomotor activity and increase in body weight are similar to the behavior of mice lacking NPY Y1 receptors.[24] Therefore, NMDAR antagonism would interact with leptin, hypocretin/orexin, and NPY to affect appetitive and consummatory ingestive behavior and could contribute to our patient's successive eating disorders.

NMDARs Interact with the Hedonic/Motivational Mechanisms of Eating Behavior

Eating is also influenced by the sensory cues associated with food (the "liking" component of reward), as well as by motivational aspects (the "wanting" component of reward or incentive salience).[25] "Liking" denotes the organism's hedonic reaction to a sensory cue, like the sensory pleasure of sweet tastes. This hedonic impact of reward implicates opioid, cannabinoid, and γ-aminobutyric acid transmission from the brainstem to the nucleus accumbens, ventral pallidum, insular cortex, and orbitofrontal cortex.[26,27] In contrast, "wanting" corresponds to the organism's motivation, behavior selection, and switching of attention toward reward-related stimuli like food (incentive salience).[28] Motivated eating is associated mainly with dopaminergic signaling in mesolimbic structures like the VTA, hypothalamus, amygdala, nucleus accumbens, and prefrontal cortex, including the medial prefrontal cortex.[29–31] Compulsive behavior, such as compulsive eating, would then result from a dysregulation of the hedonic and/or motivational networks in vulnerable persons.[26,32,33]

Several animal studies have shown that NMDA transmission participates in the hedonic/motivational mechanisms of eating behavior. NMDAR antagonism suppressed transmission of taste afferents in the cortical taste area (insular cortex) in rats[34] and was deleterious for nondeclarative taste memory in mice.[35] In addition, NMDAR blockade in the amygdala and the insular cortex prevented the attenuation of gustatory neophobia in rats, which showed a persistent and undiminished neophobic response to an initially novel taste.[36] Such findings could explain our patient's persistent dysgeusia and food phobia during her anorexic phase, when she said that every food tasted like "stool." These symptoms could help establish a situation in which reduced intake of food was at first rewarding.[37]

NMDARs are present in presynaptic terminals of projections from the hippocampus to the nucleus accumbens,[38] and can be found postsynaptically in neurons of the nucleus accumbens and in afferent projections originating in the cortex.[39] NMDARs in the nucleus accumbens shell are capable of altering dopamine, opioid, and γ-aminobutyric acid levels,[40,41] and these interactions may play a role in the effects generated by NMDA stimulation on eating and motivation. Administration of NMDA (1 µg) into the nucleus accumbens shell of rats significantly and dose-dependently increased their food intake over 4 hours[41]; in contrast, high doses (2 µg) of the NMDA antagonist MK-801 in the same area decreased the motivation to eat.[42] This mechanism could have contributed to our patient's anorexia.

NMDARs have been implicated in other mesolimbic reward sites. NMDAR blockade in the lateral/basolateral amygdala and medial prefrontal cortex strongly disrupts rats' ability to learn to press a lever to get food,[43] whereas VTA NMDAR stimulation is considered necessary for the acquisition of reward-related learning.[44]

The Role of NMDARs in Central and Peripheral Structures Related to Food Intake

NMDAR blockade in the nucleus of the solitary tract, which is considered a satiety center,[45] has resulted in increased food intake in rats[2,7] and inhibition of satiation signals exerted by cholecystokinin.[46] A similar effect has been produced with NMDAR blockade in the hepatic portal vein.[4] Actually, both central NMDARs (in vagal afferent endings in the hindbrain) and peripheral NMDARs (in the gastrointestinal tract) seem to participate in the control of food intake.[47]

However, feeding also seems to be modulated by NMDA transmission in the lateral hypothalamus. This structure is implicated in feeding mainly through interactions of its orexin-concentrating and melanin-concentrating hormone neurons with the NPY neurons of the arcuate nucleus and with the brain reward centers.[25] More specifically, orexin receptors are expressed at the surface of VTA dopamine neurons,[48,49] and this lateral hypothalamic-VTA projection is involved in food-seeking behaviors.[50] It has been found that antagonism of NMDARs in the lateral hypothalamus significantly decreases food intake.[3,8]

Potential Treatments for Eating Disorders in Humans

The implication of NMDARs in human eating behavior suggests possible new treatments for eating disorders like anorexia nervosa and bulimia nervosa. Memantine, a low-affinity NMDA antagonist, and riluzole, a noncompetitive NMDA antagonist,[51] have been shown effective in treating binge eating disorder[52–54]; ketamine, a high-affinity NMDA antagonist, has significantly decreased compulsive behavior in anorexia nervosa.[55] The exact mechanism and selectivity of these medications for specific symptoms of eating disorders are difficult to predict. However, it seems that NMDA antagonism alleviates compulsive eating behaviors by selectively interacting with the hedonic/motivational mechanisms of eating behavior.

CONCLUSIONS

Several studies have elucidated the role of NMDA transmission in the control of food intake in animal models,[3,7] and our case report supports a similar role in humans. The framework implicating NMDA transmission in the control of food intake in humans should take into account the interactions of NMDARs with the neuroendocrine and reward systems in the central and peripheral structures related to feeding and satiety.

Not all patients with anti-NMDAR encephalitis have eating disorders. The specificity of our patient's eating disorders indicates that a combination of central and peripheral modulations related to NMDAR antagonism is required to produce anorexia or hyperphagia. Further research is needed to explain the mechanism, role, and topography of NMDARs in the control of humans' food intake. That understanding could help us develop new treatment possibilities for eating disorders.

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