

# The role of the N-methyl-D-aspartate receptor in functional bladder disorders

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**Abstract:** The N-methyl-D-aspartate receptor (NMDAR) has the properties to act as ion channel and ever was considered to play an important role in learning, memory and development of pathological pain. Recent researches showed that NMDAR may be associated with the occurrence of some visceral inflammation, for example, in bladder and colon inflammation (cystitis and colitis) which were proved to be associated with some neural and auto-immune factors. In this review, the latest studies about the role of NMDAR in the lower urinary tract disease and symptoms with bladder inflammation hypersensitivity are discussed. Furthermore, we summarized the possibilities of future applications of NMDAR inhibitors in the treatment for the functional bladder disorders.

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## 1. Introduction

A number of studies reported the significance of neurotransmitters of excitatory amino acid receptors (EAARs), especially the N-methyl-D-aspartate (NMDA) receptor in transmission of nociceptive information [1-5]. NMDA does not only play a very important physiological role in the development of neural system, but also affects the formation of the neuronal circuit [1, 6]. Therefore, NMDAR is a key receptor for learning and memory. The latest further researches on NMDA showed that it also mediates the visceral hyperactivity in irritable bowel syndrome (IBS) [6]. The epidemiological studies showed that IBS and interstitial cystitis (IC) share the same visceral hypersensitivity syndromes, and the function of NMDAR in bladder disorders was also been demonstrated recently. Overactive bladder (OAB) always occurs with IC and has some similar syndromes, for example urinary frequency and urgency. NMDA glutamatergic transmission was also proved to be necessary in some neurogenic overactive bladder symptoms [6-9]. This small review describes the function of NMDA in these urinary disease and symptoms, as well as provide the future studies that aim to new treatment related to NMDAR pathways.

## 2. NMDAR function in bladder pain syndrome / interstitial cystitis (BPS/IC)

Interstitial cystitis is a chronic inflammatory nonbacterial cystitis which often attacks both in male or female. Patients may experience the protracted course of urinary urgency, urinary frequency and tenderness, or intense pain in the bladder and pelvic area. It may have a major impact on just about every aspect of patients' lives. The cause of interstitial cystitis remains not clear, which create a challenge to develop the effective standard therapy for a collection for symptoms that would derive, including bladder overactivity and painful urination with or without pelvic discomfort which has a torturing influence on life quality of about millions of people in the U.S. every year [1, 6, 8]. Although we know in bladder wall caused by inflammation and contraction of muscles in the bladder wall at the wrong time trigger the hypersensitivity of bladder, the mechanism for refractory bladder cystitis remains not clear. A variety of evidence indicated the important role of NMDAR in transmission of nociceptive information. NMDA glutamatergic transmission was also proved to be significant in some neurogenic bladder activities. These preliminarily results suggested nociceptive stimulus produced by IC might activate the NMDA receptor to transmit nerve impulse to brain, and furthermore aggravate OAB. Recent studies proved the effective role of NMDA receptor on smooth muscle and cell structure of bladder wall. MK-801 is a kind of non-competitive antagonists for the NMDAR complex, which can bind the ion

channel and furthermore block cation flow. The ion channels always keep open dependently for antagonists because of the binding of MK801, which blocks NMDAR [8, 9]. Therefore, MK801 is an important agent to study the NMDAR pathway in IC animal model. It is reported that MK801 can decrease the micturition frequency and increase the urodynamic parameters in the LP-805 urine-induced rat cystitis model. NMDAR may play a role in overactive bladder secondary to cerebral infarction [8]. There is a dose-dependent effect of MK801 on the cystometrogram in IC rats. The inhibitor of NMDAR has also been proved to contribute to the recovery of the bladder function in the pharmaceutical chemistry induced the IC model. Blocking the NMDAR by MK801 can improve the bladder function of IC animal model, such as, cyclophosphamide (CYP) model. CYP is an oxazaphosphorine alkylating agent which has been widely used for cystitis characterized by urinary frequency, hematuria, and bladder fibrosis, necrosis in animal model and also to induce the overactivity in animals. After the injection of CYP, there was a significant decrease in intermicturition intervals and increase in bladder weight and thickness of bladder wall, which are conformity with previous studies. MK801 reversed these behaviors and physiological index, which shows the blockage of NMDAR, and contributes to the recovery of bladder function. Based on histological study, the urothelium layer was seriously destroyed in CYP-cystitis rat bladders, but restored by MK801 which made this destroy reconstruct near to the level of control group.

### **3. NMDAR function in Neurogenic and term detrusor bladder overactivity**

The function mechanism of NMDAR had been studied for the role in the visceral inflammation. In vascular tissue, MEK/MAPK pathway can be activated by NMDAR-induced high nitric oxide (NO) product, which results to the presser response in rat. In CYP-treated rat bladder, iNOS also has a high expression in urothelium, which creates a good situation for presser response in bladder [6]. However, no data is available to show the possibility that blockage of NADAR can inhibit the MEK/MAPK pathway with decreasing the importation of nociceptive information. Thus, NMDA may work in the other way. In recent year, the function of collage on detrusor bladder activity was demonstrated, and the inhibition of Akt activity will

decrease NGF-induced collagen expression in bladder smooth muscle and in some studies, MK801 increased the collage expression in CYP-treated rats in the same time Akt expression was also inhibited. High expression of collagen type 1 represents for increased bladder hypertrophy in CYP-induced cystitis rats. This kind of aggravated pathological tissue fibrosis decreases the contraction function of bladder. MK801-treated rats had lower collagen type 1 expression, increased in intermicturition intervals and decreased in bladder peak pressure, so this showed blockage of NMDAR is a good way to improve bladder function for IC patients. NMDA pathway also has a functional role in bladder smooth muscle contraction [6, 8]. Patients who have IC with OAB always experience sudden and involuntary pelvic-floor contractions. CYP attenuated bladder smooth muscle contraction induced by muscarinic receptor compared to control group, while MK801 increased the contraction. Previous research demonstrated that NO produced by urothelium inhibit the rat detrusor contraction after CYP treated. In some latest researches, it is very important to note that the destroyed structure of urothelium by CYP was restored by MK801. To considerable degree, damage for urothelium by CYP depends on NO production in bladder. NO activates the NMDA pathway in turn aggravate the damage of urothelium. MK801 enhanced the contraction function by blocking NMDAR in cystitis. In addition, NO and NOS can be proved to involve in all the development process of IC and OAB caused by IC. However, interaction mechanism is not very clear until more studies on NMDA being conducted. There has been the evidence of interaction between NMDAR and NOS trigger a series of decline in bladder function.

### **4. The role of blockage of NMDA pathway on the therapy of IC and OAB in the future**

The use of NMDAR antagonists is very limited in clinic due to serious side effects on nerve system. Recent study has showed that the NMDAR might be a solution for this problem. NMDAR-induced hypersensitivity was inhibited without adverse reaction to nerve system just by uncoupling some functional amino acid of enhancer protein of NMDAR [10]. This provides a new approach to treat IC though inhibit NMDAR. It suggested that study on different urological treatment is a feasible pathway in individuation [11], and the treatment of refractory OAB can also follow this

way. NMDA receptor relates to multiple signal pathways and is mediated by several molecular during the transmission of nociceptive information, so individual treatment which is specifically designed for NMDA receptor related genes is possible to be fulfilled. Traditional antibiotic therapy for IC and OAB often focuses on the urinary tract infection but limit to having a stable effect [12-14]. From the data of animal experiments, NMDA receptor can be considered as one of new targets for the treatment of functional bladder disorder.

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