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Novel Therapeutic Approach for Neurogenic Erectile Dysfunction: Effect of Neurotrophic Tyrosine Kinase Receptor Type 1 Monoclonal Antibody

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Abstract

Background: Erectile dysfunction (ED) is a major health issue in aged populations, and neurogenic ED is particularly difficult to treat. Novel therapeutic approaches are needed for treatment of neurogenic ED of peripheral origin.
Objective: To investigate the therapeutic effects of a neurotrophic tyrosine kinase receptor type 1 monoclonal antibody (TrkA-mAb) on erectile function and sexual behavior in a rat model of cavernous nerve injury (CNI).
Design, setting, and participants: In one experiment, 84 male rats were randomly assigned to seven groups. The groups underwent either CNI or sham surgery, subsequent injection into the major pelvic ganglion (IMPG) of phosphate-buffered saline (PBS), an immunoglobulin G (IgG) control, or TrkA-mAb, and then intracavernosal (IC) injection of either PBS or varying TrkA-mAb concentrations immediately after surgery and then 1 wk later. Erectile function was assessed and histologic/molecular analyses were performed at 6 wk after surgery. In a second experiment, 36 male rats were randomly divided into three groups. The groups underwent CNI or sham surgery and then IC injection of PBS, IgG, or TrkA-mAb immediately after surgery and for 5 wk thereafter. At 6 wk after surgery, the performance of the rats in sexual behavior tests was videotaped.
Intervention: CNI or sham surgery; IMPG of PBS, IgG, or TrkA-mAb; IC injection of PBS or TrkA-mAb.
Outcome measurements and statistical analysis: The intracavernous pressure response to cavernous nerve electrostimulation was measured and midpenile cross-sections were histologically examined. Western blotting (WB) of cavernous tissue protein was performed. Rats were assessed for chasing, mounting, intromission, and ejaculation behaviors during sexual behavior tests. The data were analyzed using one-way analysis of variance followed by the Tukey-Kramer *t* test.

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Results and limitations: Recovery of erectile function of varying degrees was observed in the TrkA-mAb groups. TrkA-mAb treatment significantly suppressed tyrosine hydroxylase–positive nerve fibers in the corpus cavernosum and enhanced neuronal nitric oxide synthase–positive fibers in the dorsal nerve. The ratio of smooth muscle to collagen in the corpus cavernosum was significantly improved in TrkA-mAb treatment groups compared to PBS vehicle and IgG control groups. WB confirmed these biological changes. There was a nonsignificant increase in the average number of intromissions and ejaculations in the TrkA-mAb group. The study limitations include small sample size, variability in sexual behavior, lack of data on the neuromuscular mechanism involved, and lack of information of the role of neurotrophins or cytokines in regeneration.
Conclusions: TrkA-mAb successfully inhibits sympathetic nerve regeneration, leads to parasympathetic nerve regeneration, and has therapeutic effects on ED and sexual behavior disorder in a rat model of CNI.
Patient summary: This report provides strong evidence that a neurotrophic tyrosine kinase receptor type 1 monoclonal antibody (TrkA-mAb) inhibits sympathetic nerve regeneration, leads to parasympathetic nerve regeneration, and has therapeutic effects on erectile dysfunction and sexual behavior disorder in a rat model of cavernous nerve injury. The results raise the possibility that human patients with neurogenic erectile dysfunction may respond to TrkA-mAb in a manner that parallels the response seen in our rodent study.

1. Introduction

Erectile dysfunction (ED) affects 5–20% of men worldwide, and neurogenic ED caused by neurologic injury is particularly difficult to treat [1,2]. Even with the advent of nerve-sparing procedures, patients undergoing radical prostatectomy are at especially high risk of cavernous nerve injury (CNI) and subsequent neurogenic ED or sexual behavior disorders [3]. Phosphodiesterase type 5 inhibitor therapy, commonly used as first-line treatment for ED, remains largely inefficient in this population, and novel therapeutic approaches are needed [4].

Sexual behavior is a complex combination of highly stereotyped activities that are influenced by a variety of factors including erectile function [5–8]. In male rats, sexual behavior includes chasing, mounting, intromission, and ejaculation activities [9]. Erection plays an important role in these sexual behaviors, especially during intromission and ejaculation [5,10–12].

The mechanism of penile erection is well studied. The initiation, maintenance, and rigidity of penile erection are under parasympathetic and somatotopic control, while loss and suppression are under sympathetic control [13]. Given this dichotomy, previous functional studies suggest that elevated sympathetic tone may be one cause of some subtypes of impotence, which ultimately lead to sexual behavior changes [14,15].

Recent advances in our understanding of growth factor neurobiology have heightened clinical interest in the development of protective and regenerative neuromodulatory strategies targeting traumatic cavernous nerve recovery [16]. Neural growth factor (NGF) is a multifunctional secreted polypeptide in the neurotrophin family, along with brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and NT4/5. NGF plays an important role in the growth, maintenance, and survival of certain target neurons, especially in acute and chronic nerve injury states [17]. NGF binds to two classes of transmembrane receptors: the 140-kDa eurotrophic tyrosine kinase receptor type 1 (TrkA) and $p75^{NTR}$, a 75-kDa glycoprotein receptor [18]. Studies using gene-targeted mutant mice demonstrated that NGF and TrkA are required for the development and survival of sensory and peripheral sympathetic neurons in late embryonic and postnatal stages [19,20].

Recovery of erectile function following CNI is a slow process. The pathophysiological consequences of CNI include recovery of both sympathetic and parasympathetic nerves merged in the cavernous nerves. Our previous study demonstrated that tyrosine hydroxylase (TH), an indicator of sympathetic activity, was overexpressed after CNI in a rat model [21]. Theoretically, overgrowth of TH-containing sympathetic nerve fibers might cause excessive contraction of penile smooth muscles, resulting in ED and ultimately sexual behavior dysfunction. Prior reports support this hypothesis, as tyrosine kinase inhibition correlates with improved erection function [10,22,23]. The sympathetic nerves serve as antagonists to erections, so we hypothesized that a specific TrkA monoclonal antibody (TrkA-mAb) might block the regeneration of peripheral sympathetic neurons after CNI and pathophysiological hyperplasia induced by the neurotropic effect of the Trk/NGF pathway. The aims of this current in vivo study were to determine the neuromodulatory effect of TrkA-mAb on erectile function and sexual behavior in a rat model of CNI and to develop a novel antibody-based therapy for ED.

2. Materials and methods

2.1. Experimental design

All experimental animals were obtained from Charles River Laboratories (Wilmington, MA, USA) and kept in 12 h light/12 h dark lighting cycle with food and water freely available. TrkA-mAb was manufactured by Eli Lilly and company (a mouse monoclonal antibody with high affinity for rat TrkA [$K_D = 4.95 \times 10^{-10}$ M] and a plasma half-life of $t_{1/2} = 9.3$ d in rat). All procedures were approved by the Institutional Animal Care and Use Committee at the University of California, San Francisco.

In the first experiment, 84 male Sprague Dawley rats (12 wk old) were assigned to seven groups ($n = 12$ per group) and subjected to CNI or sham surgery and intraoperative injection into the major pelvic ganglion