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THEORETICAL EXPLORATION ON DEVELOPMENT OF PROSTATITIS INFLAMMATORY MODELS IN DRUG DISCOVERY

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ABSTRACT

Reliable experimental animal models of human diseases are critically important for the discovery of molecular pathways, genetic influences, environmental factors, and successful management strategies for humans. Inflammation is an immune response to stimuli. It begins with activation of the innate immune system by infectious or noninfectious (sterile) stimuli, and inflammasomes act as sensors and effectors of these stimuli. We need to understand recent findings on the cause of inflammation, immune system responses, and possible results when prostate is inflamed. Animals experimentally affected by such diseases provide a unique opportunity to uncover disease associated pathways, which are complicated or even impossible to define in man. Prostatitis is an important worldwide health problem in men. Animal model(s) might be useful in elucidating mechanisms involved in the molecular pathogenesis of chronic nonbacterial prostatitis and chronic pelvic pain syndrome. Given that prostatitis might have a multifactorial etiology, several animal models with unique features may prove helpful. This Paper theoretically explored a number of experimental rodent models of prostatitis.

Keywords: Disease associated pathways, Immune system, Inflammasomes, Poly- and mononuclear cell infiltrates multifactorial etiology, Prostatitis models

INTRODUCTION

Since there are waste stimuli in urine, the possibility of microbe invasion, and the possibility of urinary tract stones with associated mechanical obstruction, the prostate is vulnerable to urinary tract inflammation.

Any of these factors are likely to play a role in prostate inflammation **[1]**. Inflammation refers to the immune system's reaction to stimuli. It begins with infectious or noninfectious stimuli activating the natural immune system, with inflammasomes serving as receptors and effectors of these stimuli **[2]**. This article examines recent research into the causes of inflammation and the consequences of prostate inflammation. Inflammation is the immune response to a particular incident, while infection is the term used to characterize pathogen invasion. Inflammation is the body's way of defending itself. This will include eliminating harmful stimuli from the body, such as pathogenic bacteria, irritant chemicals, or damaged cells, and starting the healing process. Microorganisms such as bacteria, virus, or fungus, as well as other triggers, may cause infection. That's how the host body reacts to it. When something harmful affects a part of our body, our biological reaction fights to neutralize the effect **[3]**. Inflammation, especially acute inflammation, suggests that the host is attempting to repair itself. Although chronic inflammation may display some failed attempts to digest harmful stimuli, the immune system is a flexible system that is primarily designed to protect the body.

Cause of prostate inflammation: infectious stimuli

Bacterial prostatitis is most often caused by uropathogens, mainly Gram-negative bacilli. But Gram-positive and atypical microorganisms have also been identified as causative organisms of chronic prostatitis **[4]**. *Chlamydia trachomatis* and *Trichomonas vaginalis* are among common pathogens, making chronic prostatitis a sexually transmitted disease.

Cause of prostate inflammation: noninfectious stimuli

Prostatic inflammation can be caused by a number of causes. Urine that is freely refluxed into the prostatic ducts can provide a way for bacteria to colonize. Dietary ingredients, increases in serum testosterone and estrogen levels, autoimmunity, and noxious chemical reflux in the urine are all potential causes **[5]**. Furthermore, metabolic changes such as metabolic syndrome and dyslipidemia may cause prostate

inflammation. Prostate inflammation has been linked to smoking and a high-fat diet in recent research. Smoking is linked to prostate chronic inflammation in a univariable review in the Reduction by Dutasteride of Prostate Cancer Events research **[6]**. In the baseline biopsy, current smokers were more likely to have acute and chronic inflammation. By driving the NADPH (Nicotinamide adenine dinucleotide phosphate) oxidase mechanism and producing reactive oxygen species, a high-fat diet, on the other hand, can cause oxidative stress and inflammation in the prostate gland **[7]**. High-fat diet also causes a significant increase in proinflammatory cytokines through activation of Signal Transducer and Activator of Transcription (STAT)-3 and Nuclear Factor-kappa B (NF-kappa B) pathway **[8]**. Both these pathways involved in proliferation, survival, angiogenesis, invasion and inflammation in prostate **(Figure 1)**.

Prostatitis Models

There are different modeling methods for different animal species. The first step in a good animal model is the successful study of the pathogenesis of prostatitis. At present, there is no universally accepted standard method for the immunity of prostatitis for production of animal models **[17]**. Many researchers at home and abroad use rodents as experimental animals, including Wistar rats, SD rats, Lewis rats, C57BL/ 6 mice, and NOD mice **[18]**.

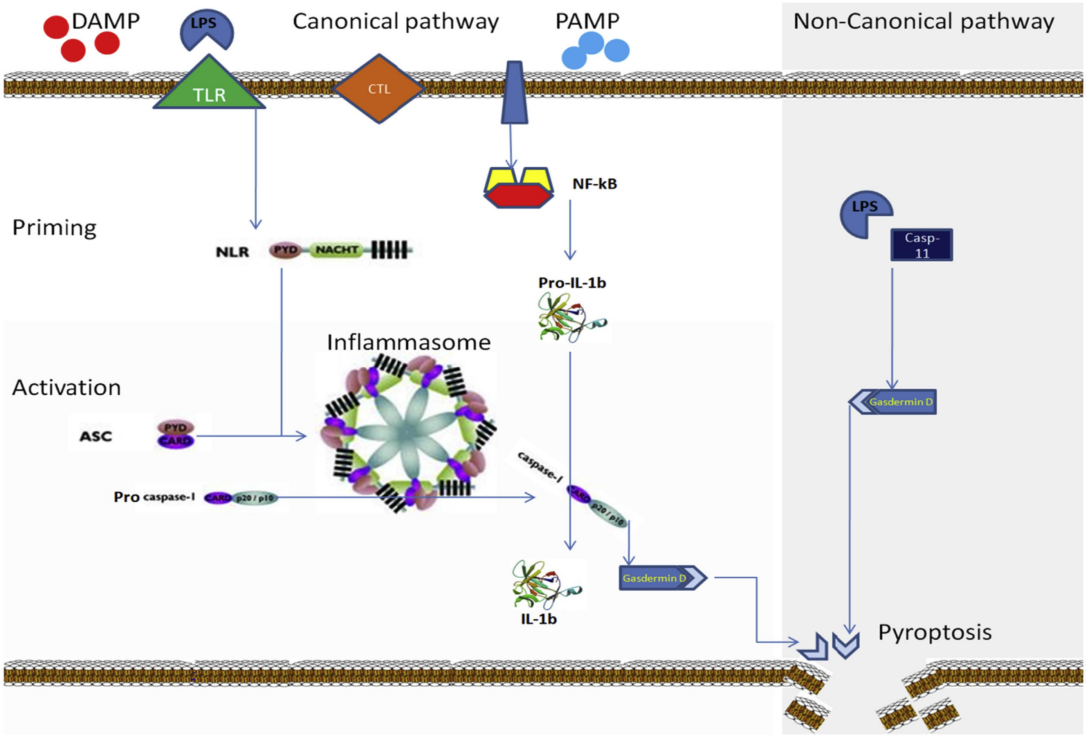

Figure 1: Components of Prostate Inflammation [35]

EXPERIMENTAL AUTOIMMUNE PROSTATITIS (EAP) MODELS

EAP Rat models

At present, there is no universally accepted standard method for the production of animal models of EAP. Many researchers at home and abroad have used rats as experimental animals **[19]**. Purified protein from the gonads of Wistar rats is used and injected complete Freund's adjuvant (CFA) into the subcutaneous tissue of the same type of rats to induce autoimmunity **[20]**. As a result, prostatitis was found in which 3 out of 8 rats (38%) exhibited a proinflammatory reaction on the 21st day after receiving a single MAG inoculation, and the same kind of rat was repeatedly tested, and 9 out of 20 (45%) showed prostate symptoms after 30 days. This classic modeling method has been used until now **[21]**. The general injection time is 0, 15 and 30 days. A total of 5 subcutaneous injections were made in the sole, inguinal and cervix of rats. The concentration of the protein purification solution was too high, which may cause the death of rats; if the concentration is too low, it is insufficient for autoimmunity.

EAP Mouse Models

The mouse model for establishing EAP was proposed by Nelson *et al*. **[22]**. They inoculated the homologous mouse's ventral prostatic lobe extract with CFA into C57BL/6 mice with a maximum dose of 0.75 mg protein extract supplemented with pertussis toxin, it was found out that 100% of C57BL/6 mice developed prostatitis with a wide range of inflammation, concentrated in the dorsal part of the prostate, and the degree of inflammation was related to the dose size. The results of SJL and A/J mice of different species were not satisfactory. It was found that SJL and A/J mice can develop some degree of inflammation. After 30 days of immunization, mononuclear cell infiltration and inflammation were found **[23]**. The site was concentrated in the interstitial and near blood vessels.

AGE-RELATED PROSTATITIS MODELS

Rat Prostatitis models

Age-related spontaneous prostatitis is a commonly used model for the study of autoimmune prostatitis. Previous studies had shown that non-bacterial prostatitis occurred spontaneously when certain ages were reached in rats of different races **[25]**. There was moderate mononuclear cell infiltration in spontaneous prostatitis, mainly CD4+T cells, and inflammation mainly occurred in the prostate interstitial, around the acinar and in the lateral lobes. The study found that these rats had a defect in their own mechanisms of tolerance to their own prostate antigens, and

as age increased and the body's environment changed, tolerance mechanisms can be further weakened, leading to age-related spontaneous autoimmune prostatitis **[26]**. The occurrence of different types of rats had a different probability of spontaneous autoimmune prostatitis.

Mouse Prostatitis models

The probability of spontaneous prostatitis among mice is small; the researchers found that aged NOD mice not only spontaneously develop autoimmunity in the pancreas, thyroid, parathyroid, and adrenal glands but also the prostate. It can produce spontaneous autoimmunity. The NOD male mice may develop spontaneous autoimmune prostatitis at 20 weeks and remain stable. This NOD mouse has type I insulin-dependent diabetes mellitus. Prostate leukocyte antigen is 2–4 times more common in these male mice than in 8-week-old mice at 20–30 weeks. By the age of 40 weeks, 70% of NOD mice will have prostatitis reaction, and both cellular and humoral immunity exist However, 8-week-old NOD mice did not show any cellular and humoral immune responses to the prostate. Studies have shown that high serum titer of IgG antibodies against prostate antigen can occur in the serum of elderly male NOD mice, with IgG2b as the major component **[25]**.

HORMONE AND CASTRATION INDUCED PROSTATITIS MODELS

Rat prostatitis models

The prostate is a well-known organ that is influenced by male hormones. Androgens are important regulators of prostate development, function, and disease. This model employs estrogen and castration to alter hormone levels and disrupt the equine androgen balance in animals, resulting in a non-bacterial inflammatory response to the prostate. In immature rabbits treated with estradiol benzoate and testosterone-stimulated adult rats treated neonatally with 17-estradiol, estrogens can induce male accessory sex organ inflammation under other conditions. The sub acute administration of estradiol-17β was shown to be a potent inducer of an inflammatory response specific to the lateral prostate of the castrated Wistar's rat. The subsequent administration of dihydrotestosterone restored the wet weight of the gland while maintaining the inflammation established with estrogen treatment These changes are histologically similar to a spontaneously arising nonbacterial prostatitis previously reported by others in the aging rat lateral prostate **[36, 38]**.

CHEMICAL MODELS

Chemicals are injected directly into the animals' prostates to induce aseptic CP in this model. Carrageenan, amidraphane, glycerin, 2% agar, formaldehyde-croton oil, FCA, and other chemicals are currently used. Carrageenan preparations are the most widely used, with the benefit of causing less damage to prostate tissue and modelling more closely resembling chronic inflammation.

It was found that SD rat intraprostatic injection of 3% carrageenan to construct the CNP model and tested its degree of reduction of the perineal pain threshold during thermal and mechanical stimulation to reflect the rat model **Figure 2**. Infiltrates of inflammatory cells, mostly monocytes and lymphocytes, fibrous connective tissue hyperplasia, interstitial hyperemia, edoema, and other chronic inflammation were seen in the model rats. The comparison between the experimental group and the control group showed that the pain threshold of the thermal stimulation was significantly reduced in the experimental group at 48–72 h, and 1 week after the injection of 3% carrageenan, and the pain threshold of the mechanical stimulation was in the injection group. After 72 h and 1 week, there was a significant decrease in the two-time points and kept a long time; the results confirmed that this method is effective in simulating pelvic floor pain. However, this modeling method also has its drawbacks. The chemical modelling approach involves injecting chemicals directly into the prostate to induce inflammation, which would eventually result in substantial damage to the prostate tissue; this model closely parallels the mechanism of prostatitis. Between acute prostatitis and chronic prostatitis, there is a distinct difference. Longer-term and long-lasting effects have not been thoroughly investigated **[36]**.

BACTERIAL MODEL

***Proteus mirabilis*-Induced Acute and Chronic Prostatitis**

Male Sprague-Dawley rats weighing about 300 g were used in this model. The rats were kept in polycarbonate box cages with corncob bedding and were kept at 20 2°C, 40% relative humidity, and 12 hours of regular lighting. Rat chow and water were given to the animals. Prior to transurethral catheterization with a lubricated sterile PE10 polyethylene feeding tube catheter, rats were anaesthetized with 4 percent halothane. A 0.2 ml bacterial suspension, prepared as described above, was inserted into the base of the prostate through the catheter. P. mirabilis strains BB2000 and KW360 were

inoculated into six rats per experimental group in three separate experiments for acute and chronic infections. On the second day after infection, animals were asphyxiated with CO_2 in the acute-infection model.

STRESS AND STARVATION RAT PROSTATITIS MODEL

Long-term planning (10 days) Prostatic inflammation is caused by stress factors such as hunger, low ambient temperature, and a small cage. Sprague–Dawley VP Irritant Rat Acute prostatitis was caused by transurethral ethanol/dinitrobenzene sulfonic acid-mediated mucosal injury, which peaked between 24 and 48 hours **[20]**.

DIET INDUCED RAT MODEL

Both a 9-week oral administration of a soy-bean extract mixture and an 11-week soy-free diet were able to induce LL/DL prostatitis in 80 percent of rat males, suggesting that the estrogen/androgen balance can play a role in initiating prostate inflammation. Prostatic Lymphocytic infiltration and interstitial edema are caused by partial mechanical obstruction of the urethra **[20]**.

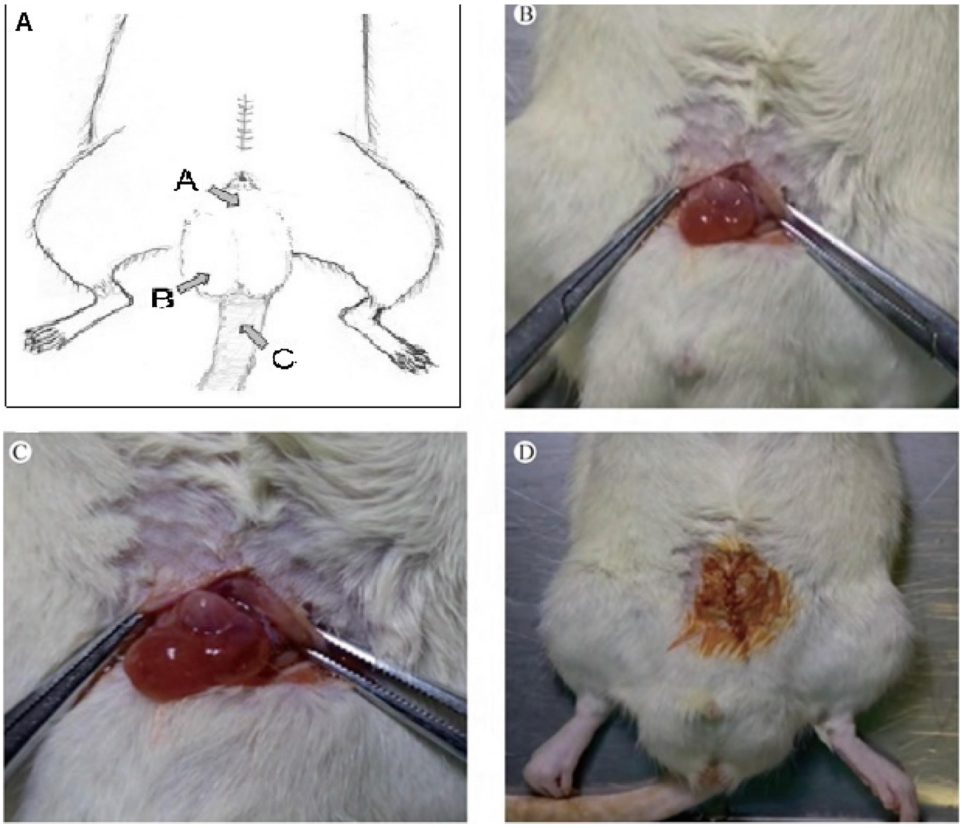

Figure 2: (A), Illustration of the pelvic areas (A), Illustration of the pelvic areas where the heat and mechanical stimuli were applied in the rat. Reductions in heat and mechanical thresholds were observed in the skin overlying the scrotum area B, but not in areas A and C. (B), the process of surgical operation to inject 3% carrageenan solution into the rat prostate lobes. Routine skin preparation and cut through the abdominal wall, and exposure of the anterior surface of the prostate. (C), bilateral injection of carrageenan solution or saline into the prostate lobes. (D), suture of the surgical incision and local use of antibiotics [38]

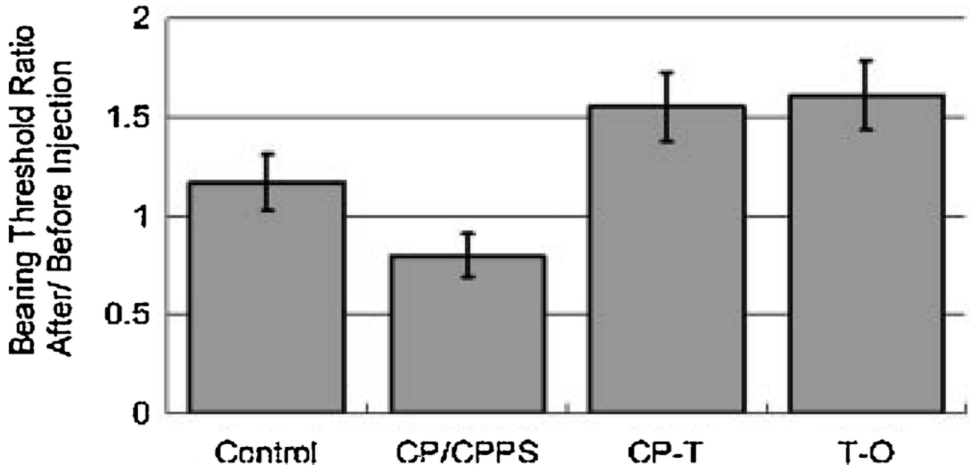

Figure 3: Mechanical allodynia confirmed by von Frey filament examination. The chronic pelvic pain was shown in the rat after prostate injection with carrageenan .Bearable pressure ratio was reduced by 32.8% in rats with CP/CPPS. With a synchronous injection of CHA solution, the rats had similar bearable pressure ratio as the controls. The ratio did not change in groups with only CHA injection [38]

Table 1: Different Prostatitis Models developed and explicated in drug discovery

Sr. No.	Prostatitis Model	Observation	References
1	Experimental autoimmune prostatitis (EAP) models	Purified protein from the gonads of Wistar rats was used in rat model and homologous mouse's ventral prostatic lobe extract with CFA into C57BL/6 mice	[19],[20],[21] [22],[23]
i	EAP Rat models	The concentration of the protein purification solution was too high, which may cause the death of rats; if the concentration is too low, it is insufficient for autoimmunity	[22],[23]
ii	EAP Mouse Models	100% of C57BL/6 mice developed prostatitis with a wide range of inflammation,	[22],[23]
2	Age-Related Prostatitis Models	Commonly for the study of autoimmune prostatitis.	[25],[26]
i	Rat Prostatitis models	The rats had a defect in their own mechanisms of tolerance to their own prostate antigens	[25],[26]
ii	Mouse Prostatitis models	By the age of 40 weeks, 70% of NOD mice will have prostatitis reaction, and both cellular and humoral immunity exist	[25]
3	Hormone and castration induced prostatitis models	Androgens play a key role in regulating the growth, function, and disease of the prostate	[36],[38]
i	Rat Prostatitis models	The sub acute administration of estradiol-17β was shown to be a potent inducer of an inflammatory response specific to the lateral prostate of the castrated Wistar's rat.	[38]
4	Chemical Prostatitis Model	Intraprostatic injection of 3% carrageenan to construct the CNP model Longer and long-lasting effects have not been studied in depth.	[36],[38]
5	*Proteus mirabilis*-Induced Acute and Chronic Prostatitis	The acute and Chronic infection model, animals were asphyxiated with CO2 on day 2 following infection, prostates from chronically infected animals were collected on 8th day post infection.	[38]
6	Stress and Starvation Rat Prostatitis Model	starvation, low surrounding temperature, and small cage 10 days long term stress and starvation induces prostatitic Inflammation	[20]
7	Diet Induced Rat Model	9 week oral administration of soy been extract mixture and 11 week soy-free diet were able to induce prostatitis in 80% of rats	[20]

DISCUSSION

There are several animal models of prostatitis developed in the past; including spontaneous, infectious models, hormone- and immune-induced, and some other models **[38]**. However, in most of these animal models, considerable attention has been focused on studying the basic histopathology and inflammatory mechanisms, not characterizing the pain behavior caused by inflammatory prostatitis **[39]**. Recently, some researchers started to pay attention to the pain behavior in animal models. The methodology using von Frey fibers to quantify tactile allodynia in a murine model of bacterial prostatitis **[40]**. Chemical irritations such as formalin, capsaicin, dinitrobenzenesulfonic acid and ethanol have been used to establish animal models of chronic prostatitis/Chronic pelvic pain syndrome (CP/CPPS) by intraprostatic injection **[41]**. Different from these chemicals, 3% l-carrageenan can cause chronic reductions in threshold to heat stimulus and mechanical stimulus in rats without excessive tissue damage **[42]**. These animal models can be used more efficiently in drug discovery to combat infections as prostatitis **[43]**.

CONCLUSION

There is currently no widely accepted standard approach for producing animal models of prostatitis immunity **[44]**. Sprague–Dawley, Wistar rats, SD rats, Lewis rats, C57BL/6 mice, and NOD mice were all used as laboratory animals by several scientists **[45]**. The current models can be a useful preclinical method for researching the neurobiological mechanisms of male chronic pelvic pain **[46]**. Stress and starvation induced model will be one of the best model of prostatitis inflammation in drug discovery process.

RELEVANT CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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