



Development of nanotechnology in andrology

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Abstract: Since first introduced in 1980s, nanotechnology has always been the eye-catching point as its providing us with new approaches to explore the microscopic world. Many nanotechnology-associated novel technologies have been brought into clinical use in the past decades and uncountable patients benefited from them, which convinces us of a bright prospect of nanotechnology in the field of medicine. In this review, literatures concerning nanotechnology applications in andrology were retrieved and we made a comprehensive discussion on drug delivery, gene therapy and stem cell therapy use in andrology, which calls for the engagement of nanotechnology.

Keywords: Nanotechnology; nanoparticle; erectile dysfunction (ED); premature ejaculation (PE)

Submitted Dec 25, 2019. Accepted for publication Jan 16, 2020.

doi: 10.21037/tau.2020.01.18

View this article at: <http://dx.doi.org/10.21037/tau.2020.01.18>

Introduction

Nanotechnology, benefited from the progression of microphysics that takes insight into materials on atom level, provides us with a new tool to explore the disease mechanism and new treatment strategy and new diagnostic method on nanoscale. It has been the hot point in the field of translational medicine for many years. Nanoparticles are defined as the materials whose scale ranges between 1–1,000 nanometers. With the characteristic of high surface area-to-volume ratio, flexible construction and relative biocompatibility (1), nanoparticle makes it possible to insert therapeutic effect precisely. Erectile dysfunction (ED) and premature ejaculation (PE) are the most common forms of sexual dysfunction for males. It was reported 9–29% men were bothered with alteration in sexual function (2). At least 20% of men had the experience of PE (3) and, among men aging between 40 and 70 years old, the occurrence rate of ED could be as high as 52% (4). However, the current available therapeutic option for ED and PE have not been

updated for years, which include oral phosphodiesterase-5 (PDE-5) inhibitors, intracavernosal injection therapy, extracorporeal shock wave therapy (ESWT), vacuum constriction devices, penile prosthesis transplant for ED and selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI) for PE. Almost all of the current therapies have some obvious shortcomings, concerning the effectiveness, safety and side effects, making it far beyond satisfactory for patients. In this review, nanotechnology associated novel treatment including drug delivery, gene therapy and stem therapy for ED and PE were summarized as to their limitation and advantages.

Drug delivery

PDE-5 is including tadalafil, sialorphan, avanafil are widely used in patients with ED for its ability of competitively binding and inhibiting PDE-5 isoenzyme. All of the current used PDE-5 are administered in oral approach for

their poor aqueous solubility, which could result in low bioavailability and systemic side effects like facial flushing, headache, nasal congestion and dyspepsia (5) and need to be noted before prescription. As one of the most commonly used pharmacy for PE, dapoxetine, a kind of SSRIs, could reach a peak of serum concentration in a short period (after ~1.25 h) and the elimination half-time is about 1.31 h (6). However, because of the existence of hepatic first pass metabolism, the bioavailability of oral administered dapoxetine could be as low as 42% (7).

With the application of nanotechnology, new approaches of medicine delivery were explored to promote the efficacy and minimize the side effects of current available agents.

Nanoparticle based transdermal delivery system

Solid lipid nanoparticles (SLNs), first developed in 1990s for oral administration (8), are characterized by their submicron size. This kind of nanocarrier-based delivery system is composed of a lipid solid matrix stabilized by a surfactant (9). In the drug delivery system based on SLNs, lipid matrix crystal voids encapsulated agents were exempted from degradation in the process of delivery and prolonged release in the targeted area was observed (10). Obvious advantages over traditional drug delivery is expected in SLNs based transdermal delivery system as it could release at the certain site, thus minimizing the side effects that could be caused by oral administration. It is theoretically safe to apply this kind of materials on skin for its phospholipids substance, which are non-toxic and non-irritant. In addition, significant decreased total trans-epidermal water loss and increased surface area in this nanoparticle conjugated delivery system enables longer residence and contact of drugs (11). Kurakula *et al.* in their study evaluated the permeation parameters and release mechanism of avanafil SLN in rat model (10). In this study, it was observed that the penetrating ability of avanafil was enhanced by SLNs, suggesting that SLNs could be an effective approach for transdermal drug delivery.

In another study, Han *et al.* explored the effectiveness of erectogenic agents including tadalafil, sialorphin, and nitric oxide (NO) in ED treatment when encapsulated by nanoparticles (12). A kind of nanoparticle based hybrid hydrogel/glass was used as the delivery system in this study. Systemic blood pressure (BP) and intracorporal pressure (ICP) were measured and continuously monitored throughout the experiment.

In the group treated with nanoparticles encapsulated

NO, initially spontaneous erection could be observed 4.5 minutes after drug, with a duration of erectile of 1.42 minutes and ICP/BP of 0.67 ± 0.14 . In sialorphin nanoparticles group, there were 4.5 minutes, 8 minutes and 0.72 ± 0.13 respectively, which were significantly different from the empty nanoparticles group. Finally, there yielded a conclusion that the topical erectogenic agents encapsulated by nanoparticle based hybrid hydrogel/glass delivery system could be useful in treating ED when applied to the penis.

Prostaglandin E1 ethyl ester was once reported being applied in a patient with systemic scleroderma. When applied with a transdermal system, a marked increase in blood flow velocity was observed (13). Nanoparticle based delivery system of alcohol hydrogels containing prostaglandin E1 ethyl ester was explored on cat model, in which the alcoholic hydrogel was used as a gel to the penis. ICP was measured to evaluate the effect of this transdermal therapy and the results indicated this delivery system might be effective as an ED treatment alternative (14).

Various liposomal nanoparticulate carriers have been put into clinical use, especially in transdermal therapy as a novel drug delivery system encapsulating those agents with poor solubility, low stability in water and poor permeability of stratum corneum (15). Liposomal nanoparticulate carriers could be subtyped into conventional liposomes (L-RSV), deformable liposomes (LD-RSV), ultradeformable liposomes (LUD-RSV) and ethosomes (Etho-RSV). Ethosomes were evaluated as vardenafil carrier *in vitro* for ED treatment. Rat model was used and the effects of lipid composition, sonication time, and ethanol concentration on particle size and encapsulation efficiency were evaluated in this study (16). Confocal laser scanning microscopy imaging technique was utilized to measure the diffusion release rate of vardenafil. A supporting result showed that the bioavailability of vardenafil delivered from transdermal pathway in nanoethosome form was approximately twofold higher than that from an oral administered aqueous suspension (16).

Nanoparticle based oral delivery system

Sildenafil is a widely used PDE-5 inhibitors for treatment of ED, which is insoluble in water. As concerned the insolubility of commercially available sildenafil tablet and the existence of intestinal and hepatic first-pass metabolism (~80% of administered oral dose) (17), the effect of sildenafil was impeded for its low oral bioavailability of the tablet (40%) and delayed onset (45 min) and short duration

of action, with a very short physiological half-life of 4 h (18). Despite of the modality of nanoparticle based transdermal delivery system, nanoparticle encapsulated sildenafil for oral delivery was also explored. SLNs was used as the carrier for oral sildenafil administration in a study conducted by Hosny *et al.* (19). Compared to the commercially available sildenafil tablet, this *in vivo* pharmacokinetic study revealed the SLNs encapsulated sildenafil with enhanced bioavailability by >1.87 fold, and the mean residence time was longer (19).

Nanoparticle based intranasal delivery system

Intranasal drug delivery system was most commonly used in local treatment for diseases like cold, cough and rhinitis. Compared to oral drug administration approach, intranasal approach exhibits characteristics of rapid onset of action, and, as the result of avoidance of first pass metabolism, higher bioavailability (20,21). However, because of the existence of nasal mucosal barrier and nasal enzyme system, it was hard to insert therapy for other organ by intranasal approach. With the utilization of nanoparticle drug delivery system that could enable efficiently transmucosal delivery and protect the agents from enzyme degradation, it has been explored to transport pharmacy into systemic circulation, thus for the treatment for disease in other organs. In the field of andrology, Fouad *et al.* produced an instantly-dispersible nanocarrier powder system (IDNPs) for intranasal delivery of dapoxetine in their study (22). This nanocarrier system was evaluated for its *ex-vivo* permeation and *in-vivo* pharmacokinetic parameters in rabbit model and compared with a corresponding oral nanocarrier administration group. Higher bioavailability (235.41% to oral group) was observed in intranasal nanocarrier group, which confirmed that even encapsulated in nanoparticles, agents could not be efficiently absorbed in oral approach due to the existence of hepatic first pass metabolism. Intranasal route, however provide with a new insight into the solution of avoidance of hepatic first pass degradation and increase the bioavailability when joined with the application of nanoparticles. In another study, tadalafil nanoemulsions were delivered in intranasal approach and evaluated for its characterization and pharmacodynamic parameters (23). Tumor necrosis factor- α (TNF- α) and caspase-3 in rat nasal tissues were assessed for nasal toxicity and cyclic guanosine monophosphate (cGMP) in rat penis 2-h post-treatment was assessed for efficacy. No significant difference in values of TNF- α and caspase-3 between the nanoemulsion treated groups and the control group and a significantly higher

level of cGMP in intranasal nanoemulsions group were observed, indicating the intranasal nanoemulsion delivery system could be safe and effective in ED treatment.

Gene therapy

Gene therapy is a promising aspect for ED treatment as it has some prominent advantages over oral therapies. Most of the oral medicines like PDE-5 inhibitors are short lived and need to be taken on-demand, which means the sexual activity need to be planned. Though some studies have explored the treatment of daily low-dose PDE-5 inhibitors and the results are promising (24,25), it requires daily drug taking and the compliance of patients could be unsatisfactory. The effect of gene therapy could last for a relatively long period for the rate of smooth muscle turnover is relatively slow in penis (26), thus making it more acceptable for those patients.

Generally, gene therapy refers to using nucleic acids to treat and control diseases. Viral and non-viral vectors are most used gene carriers for delivering foreign therapeutic genes into somatic cells (27,28). Current gene therapies in ED could be categorized into activators of the nitric-oxide system, endothelial growth factors (GFs) promoters, and modulators of ion channels in smooth muscle cells (26). The knowledge of gene therapy in ED has been expanded with the increasing understanding of the pathophysiological mechanism involved in ED. Molecular targets including nitric oxide synthase (NOS), neurotrophic and angiogenic factors, potassium channels, prostacyclin synthase (PGIS), antifibrotic factors, and peptides have been well studied in previous studies and most of these studies were conducted on animal models, concerned the safety. The results have been summarized in a recent review by Yu *et al.* (29). However, most of the studies discussed used viral vectors for gene transferring, which result in a limitation in human application for safety uncertainty. Virus vector including retrovirus, adenovirus, herpes simplex virus 1 (HSV-1), vaccinia virus, lentivirus, baculo virus, moloney murine leukemia virus (MLV proteins) and adeno-associated virus (30) were once the most widely used vector in conventional gene delivery. Though promising was gene therapy demonstrated in the field of medicine, the progress of viral vector in further clinical application was impeded for its drawback including immunogenicity, cytotoxicity, inflammatory reaction towards viral vectors and insertional mutagenesis of gene delivering viral vectors (31).

The first human trial using non-viral gene carrier for

gene therapy in ED patients was reported in 2005 (32). In this study, hMaxi-K, a kind of modulator of ion channels in smooth muscle cells was administered intracorporally. They designed a single administration of three escalating doses of hMaxi-K injected into the cavernous body. EKG, general blood electrolyte and liver chemistries, hematologic parameters, sex hormone, cortisol, thyroid profiles, urine and semen analysis was conducted to assess the safety and tolerability of hMaxi-K. Results of the study showed there was no drug related adverse event observed during six-month follow-up. Naked DNA was chosen as the gene transfer vector in this study and thus could theoretically reduce the incidence of adverse effects like immune and inflammation, which could be wide common in gene therapy using viral vector.

However, naked DNA is not widely used as the vector in gene therapy for its lack of efficiency in transfer and short duration (33).

Researchers were put into a dilemma in making the gene transferring effective and safe at the same time till the emergence of nanotechnology, which greatly boosted the application of non-viral vector. Nanoparticles, with its diameter ranging from 10 to 200 nm, are born with some eminent properties. As the size of nanoparticles is close to that of protein molecules, it could penetrate the tissue deeply and easily (34,35). On the cellular level, nanoparticles could interact with the biomolecules on the cell surface or inside cell, making it possible for a targeted gene delivery (36). Several delivery tools have been designed based on different nanoparticles, such as magnetic nanoparticles, carbon nanotubes, liposomes and gold nanoparticles (37,38). Though previous studies using viral vectors have demonstrated the effectiveness of gene therapy in ED in animal model, there is no experiment performed using non-viral vector based on nanoparticle, which could be the next step of value to be explored.

Stem cell therapy

Stem cells, defined as those cells with self-renewal ability and the potency of multi-differentiation, are now widely used in the field of medicine. In recent years, stem cell therapy has been gaining more and more attention for the treatment of ED, especially that are resulted from cavernous nerve (CN) injury. CN injury induced ED is common in patients who underwent radical prostatectomy (RP) and the morbidity of RP-induced-ED ranges from 20–93.9% according to previous study (39-41). The value

of stem therapy for ED treatment in animal model has been well studied (42-45). Most of the studies reported a positive effect of stem cell therapy on ED patients. Meanwhile, the mechanism was also studied and the most widely accepted theory could be summarized as: (I) stem cells could promote the regeneration of CN by secreting GFs in paracrine pathway (46); (II) adipose-derived stem cells (ADSC) repaired the damage of corpus cavernosum to improve erectile function by directly differentiating into cavernous endothelial cells and smooth muscle cells (47); (III) exosomes secreted by ADSC could inhibit the apoptosis of corpus cavernosum endothelial and smooth muscle cells (48); (IV) ADSC act through releasing intracellular preformed substances or by secreting certain biomolecules (49). An important hurdle that impede the clinical application of stem cell therapy in ED is the high blood clearance in penis (50), which could make it difficult for ADSCs to be retained locally. Lin *et al.*, in their study observed ADSCs exited the penis within days of IC injection and migrated preferentially to bone marrow (51). Thus, researchers explored the usage of magnetic nanoparticle to retain the magnetized stem cells in corpus cavernosum so that the stem cells could reside in the target area for a relatively long period.

Lin *et al.* performed a study to investigate the efficacy of using magnetic nanoparticles to maintain stem cells in the corpus cavernosum after intracavernous injection (ICI) in animal model (52). In this study, bilateral cavernous nerve crush (BCNC) was performed on rats to establish the ED model, which were then randomly assigned into three groups: ADSCs treated group, nano-ADSCs treated group and nano-ADSCs + magnet treated group. Cell tracking results showed that under the usage of magnetized nanoparticle, ADSCs could be retained in the corpus cavernosum for up to 3 days, compared to those ADSCs in other groups washed out by day 1 after ICI. The intracavernous pressure (ICP)/mean arterial pressure (MAP) ratio was measured to assess the erectile function and the results showed that the ICP/MAP ratio in BCNC + nano-ADSCs + magnet group (52.22 ± 5.36) was significantly higher than in BCNC + nano-ADSCs group (37.06 ± 3.94). It was concluded in this study that magnetized nanoparticles could be effective in retaining ADSCs locally in corpus cavernosum and promote the effect of stem cell therapy for ED.

In another study reported by Zhu *et al.* (53), they labeled the ADSCs with superparamagnetic iron oxide nanoparticles (SPIONs) and evaluate its effect in ED treatment in diabetic rat model. In this study, diabetic rats were assigned into 3 groups: phosphate-buffered saline (PBS) treated group,

ADSCs labeled with SPIONs treated group (ADSC group) and SPION-labeled ADSCs with magnetic field application treated group (M-ADSC group). Study results showed SPION-labeled ADSCs responded to exterior magnetic fields both *in vitro* and *in vivo* and the measurement of ICP/MAP ratio showed a significant improvement of erectile function in M-ADSC group compared to ADSC group. A similarly designed study evaluating the efficacy of superparamagnetic iron oxide nanoparticles-labeled human mesenchymal stem cells (SPION-MSCs) for ED treatment by transplanting SPION-MSCs into the CN injured cavernosa of rats was reported by Kim *et al.* (54). Results showed that SPION-MSCs treated group exhibited better erectile function according to the ICP/MAP ratio and a significant longer existence of transplanted SPION-MSCs for up to 4 weeks was confirmed in SPION-MSCs treated group (54). These findings suggest the application of magnetic nanoparticles bound to ADSCs could be an effective approach in retaining the stem cells in therapeutic target and promote its therapeutic efficacy. Long-term study results on the safety and tolerability of magnetic nanoparticles conjugated stem cell *in vivo* were needed for further discussion.

Conclusions

In this review, we take a look into the application of nanotechnology in andrology, especially in the treatment for ED and PE. Traditional treatments like PDE-5 inhibitors, SSRI and newly emerging treatments like gene therapy and stem therapy are all far beyond fantastic therapies for their systemic side effects, risk of immunogenicity, cytotoxicity, inflammatory reaction and lack of targeting. Nanotechnology provides us with a method to ameliorate the situation. It should be addressed that most of the relevant studies were conducted on animal models and there is still a long way to go before bringing it into clinical use, which calls for long-term study results to explore its' safety *in vivo*.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau.2020.01.18>).

The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Liu SZ, Feng DC, Liu ZH, Liang JY, Ren ZJ, Zhou C, Wu K, Zhang FX, Zhang F, Lu YP, Wang XD. Development of nanotechnology in andrology. *Transl Androl Urol* 2020;9(2):702-708. doi: 10.21037/tau.2020.01.18