

THE ORIGINAL PEPTIDE COMPLEX AFFECTS THE PROSTATE TISSUE OXYGEN CONSUMPTION RATE IN RATS

Lobkarev AO^{1,2}✉, Muzhekhoev AA³, Evloev MK³, Dzhandigov RB⁴, Korigov IA⁴

¹ Kazan State Medical University, Kazan, Russia

² Mother and Child Clinic, Kazan, Russia

³ Bekbotov Nazran Central District Hospital, Magas, Russia

⁴ Republican Center for Disaster Medicine and Emergency Care, Magas, Russia

Despite the successful practice of using the Russian-made original peptide complex (OPC), the complex pharmacodynamics is poorly understood. The study aimed to assess the effect of taking OPC on the prostate tissue oxygen consumption rate (OCR) in white outbred rats. The experiments involved 65 adult male white outbred rats (age 6 months, body weight 410.8 ± 2.7 g). The rats were kept under standard vivarium condition, each in a separate cage; the diet and drinking regime were standard. The difference in animal housing was that animals of the experimental group ($n = 49$) received OPC throughout 20 days before the day of the experiment: every day 0.35 mg (0.85 mg/kg) of the drug were dissolved in 20 mL of the drinking water the animals drank from the trough. The drug was not administered to the control group ($n = 16$). A prostatectomy was performed. The prostate tissue OCR was measured using the DKTP-03 optical dissolved oxygen sensor with a thermoelectric converter. The O_2 concentration readings ($ConO_2$) in mg/L were recorded every minute throughout 60 min. Significant intergroup differences in $ConO_2$ values in the end of the experiment were found ($p < 0.05$). It has been shown that OPC increases the prostate tissue OCR in white outbred rats.

Keywords: original peptide complex, prostate, demography, oxygen consumption rate, innovations

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Kazan State Medical Academy (protocol No. 3/05 dated 06 May 2015). Animals were kept and handled in accordance with the requirements of the Declaration of Helsinki.

✉ **Correspondence should be addressed:** Alexey O. Lobkarev
Daurskaya 34A, Kazan, 420087, Russia; aolobkarev@mail.ru

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ОРИГИНАЛЬНЫЙ КОМПЛЕКС ПЕПТИДОВ ВЛИЯЕТ НА СКОРОСТЬ ПОТРЕБЛЕНИЯ КИСЛОРОДА ТКАНЬЮ ПРОСТАТЫ У КРЫС

А. О. Лобкарев^{1,2}✉, А. А. Мужехоев³, М. К. Евлоев³, Р. Б. Джандигов⁴, И. А. Коригов⁴

¹ Казанский государственный медицинский университет, Казань, Россия

² Клиника «Мать и дитя Казань», Казань, Россия

³ Назрановская центральная районная больница имени Б. Б. Бекботова, Магас, Россия

⁴ Республиканский центр медицины катастроф и скорой помощи, Магас, Россия

Несмотря на успешный опыт использования оригинального комплекса пептидов (ОКП) российского производства, его фармакодинамика изучена не полностью. Целью исследования было определить влияние употребления ОКП на скорость потребления кислорода (СПК) тканью простаты у белых беспородных крыс. Эксперименты проводили на 65 взрослых белых беспородных крысах мужского пола (возраст — 6 месяцев, масса — $410,8 \pm 2,7$ г). Крыс содержали в стандартных условиях вивария, каждую в отдельной клетке, питание и питьевой режим — стандартные. Различие в содержании животных заключалось в том, что животным экспериментальной группы ($n = 49$) давали ОКП в течение 20 дней перед днем эксперимента: ежедневно 0,35 мг (0,85 мг/кг) препарата растворяли в 20 мл питьевой воды, которую животные пили из поилки. В группе контроля ($n = 16$) препарат не вводили). Выполняли простатэктомию. СПК тканью простаты измеряли оптическим датчиком растворенного кислорода с термоэлектрическим преобразователем ДКТП-03. Показания концентрации O_2 ($КО_2$) в мг/л фиксировали ежеминутно на протяжении 60 минут. Установлены статистически значимые различия в значениях $КО_2$ на финише экспериментов между группами ($p < 0,05$). Показано, что ОКП повышает СПК тканью простаты у белых беспородных крыс.

Ключевые слова: оригинальный комплекс пептидов, простата, демография, скорость потребления кислорода, инновации

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Соблюдение этических стандартов: исследование одобрено этическим комитетом Казанской государственной медицинской академии (протокол № 3/05 от 06 мая 2015 г.). Условия содержания животных и работы с ними соответствовали требованиям Хельсинкской декларации.

✉ **Для корреспонденции:** Алексей Олегович Лобкарев
ул. Даурская, д. 34А, г. Казань, 420087, Россия; aolobkarev@mail.ru

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The demographic situation in Russia is recognized as tough [1]. This fact dictates the need to search for new remedies for conservative treatment of males suffering from prostate disorders and having the semen analysis abnormalities, since ejaculate deterioration is associated with the prostate dysfunction (to no lesser extent than with testicular dysfunction) [2–3]. The statistics on neoplastic diseases, specifically prostate cancer (PC) is also alarming; some researchers reasonably believe that the prostate tissue chronic inflammation is a predictor and factor of PC development [4–5]. There is a need for breakthrough original treatment approaches, one of which is a Russian product: the use of the original complex of peptides (OPC) of the prostate, testicles, and adrenal glands [6]. We have acquired considerable experience of its successful use in males with the bladder and prostate dysfunction associated with chronic non-inflammatory prostatitis (CNP) and benign prostatic hyperplasia (BPH), which are currently commonly referred to worldwide by the term "lower urinary tract symptoms" (LUTS). This suggests that OPC has a pharmacotherapeutic effect on the prostate tissue, since it contributes to the LUTS relief and improvement of the males' quality of life.

The today's legislative regulation of medical activities in Russia delineates the conditions and procedure for the use of substances that have the status of drugs and products that have the status of dietary supplements. The OPC considered is a dietary supplement [6]. We believe that this fact is the reason for inadequate attention from researchers to this promising product, which has disorders of the reproductive system, decreased sperm quality, as well as a wide range of LUTS among indications for prescription. In other words, OPC targets the problem of increasing the birth rate, improving the quality of life of males and their partners, contributes to active longevity, i.e. targets all the tasks that have been assigned the status of priority state importance [1]. Despite the obvious originality of the scientific research underlying the creation of the innovative OPC product, as well as rather successful experience (including our own) of using OPC in patients with CNP, the scientific literature has not yet developed a clear understanding of the factors and conditions that determine personalization of its efficacy in different people with the seemingly similar symptoms and typical medical history. According to the official product summary sheet, OPC is a combination drug. The testosterone synthesis normalization and libido improvement, restoration of prostate function, increasing the chance of becoming a father are the main OPC functions. OPC effectively prevents prostatitis, benign prostatic hyperplasia, adjusts the erectile dysfunction manifestations [6].

Our focus was also on an ancient socio-cultural phenomenon: in a number of countries in Southeast Asia and Africa, eating animal testicles is a part of the diet [7]. It must be emphasized that the birth rate in these regions of the planet is stably high.

We have hypothesized that the OPC components contain pharmacologically active substances capable of affecting the prostate tissue oxygen consumption rate (OCR), which can determine their efficacy in males when used for both preventive and treatment purposes (for example, in chronic prostatitis, benign prostatic hyperplasia, poor ejaculate quality). This set of issues still awaits its researchers.

The study aimed to assess the OPC effect on the prostate tissue oxygen consumption rate in white outbred rats.

METHODS

The experiments involved 65 adult male white outbred rats. The animals' age was 6 months, and body weight was

410.8 ± 2.7 g. Exclusion criteria: animal's weight below 350 g or over 450 g.

Rats were kept under standard vivarium conditions, each in a separate cage. The diet and drinking regime were standard. The only difference in the housing conditions of animals of the experimental and control groups was that animals of the experimental group ($n = 49$) received OPC throughout 20 days before the day of the experiment. Rats are stably in need for water, which was used for administration of the drug: every day 0.35 mg of the drug were mixed with 20 mL of drinking water the animals drank from the trough. This daily dose corresponds to 0.85 mg/kg (human daily dose).

The control group ($n = 16$) was not administered the drug. Another 49 animals (experimental group) received OPC.

The animals were divided into two groups by simple randomization. Homogeneity of the experimental and control groups in terms of body weight was determined using the Mann-Whitney U-test [8].

For premedication each animal was intramuscularly administered xylazine at a dose of 25 mg/kg. Five minutes after premedication, Zoletil-100 was intramuscularly administered at a dose of 10 mg/kg. Zoletil-100 is a mixture of tiletamine hydrochloride and zolazepam hydrochloride 1 : 1. A prostatectomy was performed under general anesthesia; immediately after that the prostate tissue was weighted and homogenized. Then 0.5 g of homogenate was placed in a beaker, which was filled with 15.0 mL of saline.

The prostate tissue oxygen consumption rate (OCR) was measured using the Russian-made DKTP-03 optical dissolved oxygen (DO) sensor with a thermoelectric converter [9]. DKTP-03 is a part of the Expert-009 DO analyzer, also manufactured in Russia [10]. The device physical and chemical operation principles are based on the Stern–Volmer equation. First, under the exposure to the purple light with the specific wavelength, molecules of the indicator substance contained in the sensor membrane, which is in contact with the liquid medium in which the sensor is immersed, become excited. Second, the more molecular oxygen (O_2) in the test solution, the faster this O_2 relieves the membrane excitement, bringing its state back to baseline. This complex of processes results in the display of the dissolved O_2 concentration readings expressed in mg/L on the device screen [9, 10]. DKTP-03 was immersed in a glass beaker so that the beaker was filled to the top with 15 mL of the 0.9% sodium chloride solution and contained 0.5 g of the rat prostate tissue homogenate obtained immediately after the prostatectomy. Then the homogenate was thermostatted at a temperature of 36.6 °C for 60 min under hermetic conditions. The DKTP-03 sensor connected to the Expert-009 unit was immersed in the beaker. It was thermostatted at a temperature of 36.6 °C while maintaining an airtight seal. The O_2 concentration readings in mg/mL were recorded every minute throughout 60 min. After that the minute-by-minute O_2 concentration readings recorded in all the experiments were entered in the table, and the minute-by-minute mean O_2 concentration values were calculated. Then the natural logarithm ($\ln$) of O_2 concentrations was calculated for that. Graphs in the "time — $\ln$ concentration" coordinate system were plotted based on these values. We assumed that the slope of the curve in the "time — $\ln$ concentration" coordinate system corresponded to the elimination rate constant, and in our case to the oxygen consumption rate [11].

RESULTS

The results are provided in Fig. 1 and 2. In the beginning of the experiments the O_2 concentration in the control group was 7.74 ± 0.15 mg/L; in the experimental group it was 7.61 ± 0.07 mg/L

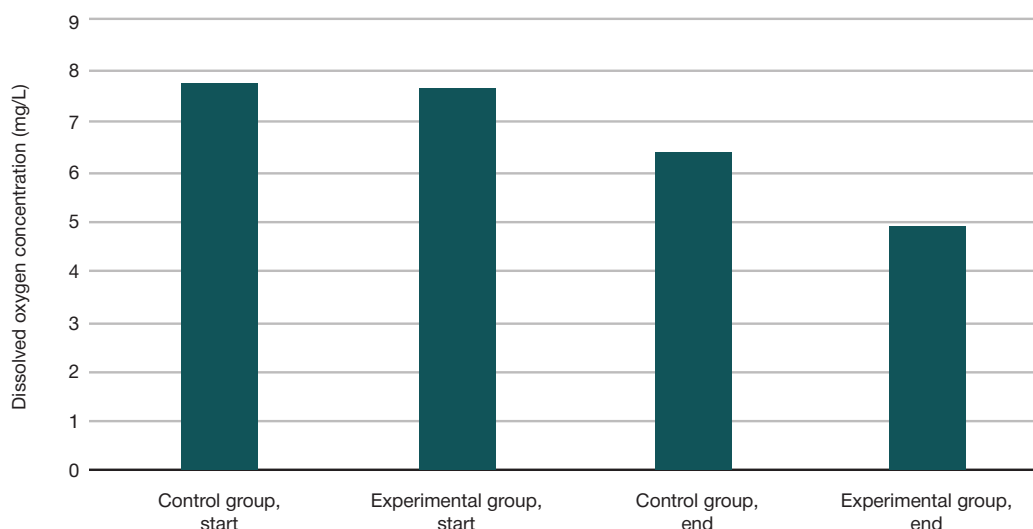


Fig. 1. Diagram of comparison of the dissolved oxygen concentrations in the beginning and in the end of the experiments for the control and experimental groups

(the standard error of the mean is given in parentheses). Statistical analysis performed using the Mann–Whitney U-test in the beginning of the experiments revealed no differences in oxygen concentration values between the control and experimental groups ($ZT = 0.69$) [8].

The following results were obtained in the end of the experiments. The O_2 concentration in the control group was 6.40 ± 0.14 mg/L; in the experimental group it was 4.89 ± 0.07 mg/L. Using the Mann–Whitney U-test it was found that there were significant differences in O_2 concentration values in the end of the experiments in the control and experimental groups ($ZT = 5.73$; this is higher than 1.96, $p < 0.05$) [8].

DISCUSSION

We believe that the pattern we have determined is interesting, since it allows us to explain a number of aspects, primarily the physical and chemical basics of the OPC mechanism of action on the prostate, from the scientific point of view. We tend to think that it is associated with intensification of metabolic processes in the prostate. As is well known, semen largely consists of the prostate secretion, which can be considered a transport medium for spermatozoa. Energy is needed to produce its components, therefore it is quite logical that OPC increases the prostate tissue oxygen consumption rate. We have found no such research in the available literature.

Second, the following is less obvious, but extremely important. In order to ensure the increased oxygen consumption, the prostate cells need to have sufficient oxygen. However, this is far from always the case. The papers by Russian and foreign urologists show that ischemia of the pelvic organs, specifically the prostate, represents an element of pathogenesis of many disorders, which include chronic prostatitis, benign prostatic hyperplasia (BPH), and chronic pelvic pain syndrome [2, 3, 12, 13]. And here's the dilemma: if the prostate cells have sufficient oxygen (no ischemia), the OPC efficacy would reach its maximum; if the prostate tissue functions under the conditions of ischemia, the drug efficacy for LUTS would be low – up to completely no effect. It is from these scientific positions that we tend to explain the personalized drug efficacy, which varies over a wide range.

A practical recommendation can be deduced from the above: to conduct an in-depth study of factors that may cause pelvic ischemia before prescribing the drug to patients. In particular, such study can involve Doppler ultrasound examination of blood vessels, contrast-enhanced pelvic magnetic resonance tomography, etc.; this can make it possible to predict the OPC efficacy.

In this context, we consider it necessary to point out that such patterns of the effects on the prostate tissue OCR have been earlier reported for doxazosin and tadalafil [14, 15]. Thus, the α -adrenergic blocker doxazosin increases the rat prostate

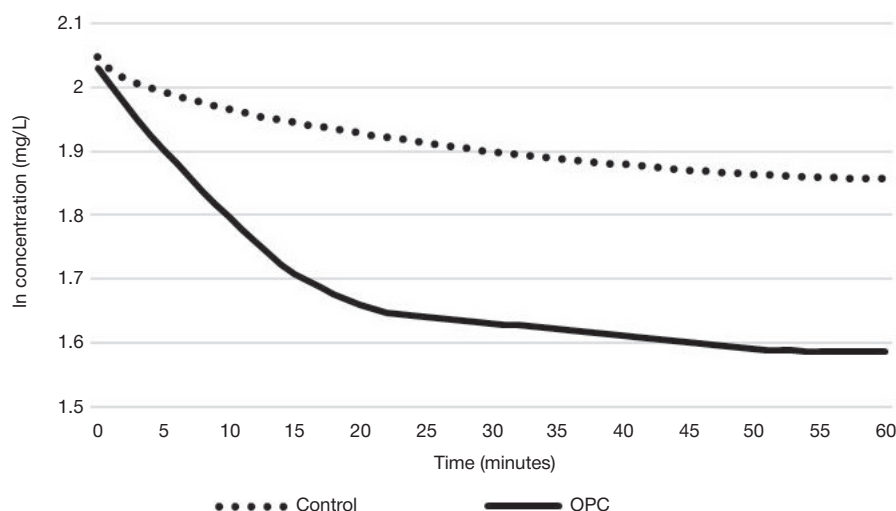


Fig. 2. Dynamic changes in the prostate tissue oxygen consumption in the rats receiving the original peptide complex

tissue oxygen consumption rate [15]. This pharmacological effect of doxazosin can hardly be considered as expected or “logical”. After all, as is known, the adrenergic system mediates stress responses. Doxazosin is an — 1-adrenergic blocker, so it seems to be more logical to expect, that it would decrease the oxygen consumption rate. That is why we believe: the fact that doxazosin increases the oxygen consumption rate is interesting [15]. In our opinion, this phenomenon may indicate that doxazosin has a different mechanism underlying the effect on the prostate tissue realized by means of the unknown biochemical processes. At the same time, this possible unknown mechanism of action and the classical — 1-adrenergic blocking effect on the prostate can co-exist and explain, why the effects of doxazosin in patients with BPH and CP are individual [15].

The tadalafil mechanism of action on the prostate is still considered to be poorly understood, because there is no phosphodiesterase type 5 enzyme in the prostate (in contrast to the penile corpora cavernosa, where it predominates) [12, 13]. This issue has been the subject of debate among urologists for years. However, there is a trend towards expansion of indications for the use of tadalafil [13]. In this context, the findings of our study focused on OPC are interesting, which suggest the need for further research to expand the indications for its use.

It is necessary to specify the limitations of the experimental model used. It is well known that the results of the studies involving laboratory animals can be extrapolated to humans considering the assumptions that there are similar physical and chemical patterns of oxygen diffusion in tissues of the human body. It should also be noted that such studies involving the human prostate are hardly possible due to ethical and legal reasons. However, here we must pay tribute and respect to the classics of experimental biology and medicine, who established the postulates that today form the basis of every physician's training using animals [16–19].

Over the course of 20–30 years, papers by the research teams that consider oxygen consumption not only as a process localized in the mitochondria have also gained popularity. Thus, the school of thought of Professor V. P. Skilachev is

known for its studies of “membrane bioenergetics”; one major postulate is that any semipermeable membrane provides the basis for energy condensation, at least due to the difference in concentration of various ions on both membrane sides. Therefore, the process of ion transfer through membranes can be a source of energy for doing work [20]. It should be considered that our contemporaries are developing the ideas of another luminary of the past, Walther Nernst. And here these thoughts are organically and consistently combined with the works of Professor V.Kh. Khavinson: he postulated the principle of strict targeting, according to which the peptides obtained from certain organs are capable of interacting with proteins of the same organs, albeit from other types of organisms, via protein–protein contacts [21]. These processes modulate metabolism and energy consumption.

Many experts consider the ability of the prostate peptides to improve blood microcirculation as one of the main determinants of their efficacy [22–24].

CONCLUSIONS

The experimental study involving white outbred rats has shown that the OPC increases the prostate tissue oxygen consumption rate, which suggests improvement of its metabolism and oxygenation. Extrapolation of the data obtained to the human body makes it possible to explain the OPC mechanism of action in individuals with the lower urinary tract symptoms associated with benign prostatic hyperplasia and chronic prostatitis, as well as in individuals with impaired spermatogenesis. It can be assumed that the OPC individual clinical efficacy for lower urinary tract symptoms can result from medical and biological differences between patients, specifically by the varying severity of pelvic organ ischemia. We believe that our results can knit together the theory of oxygen supply to the body, issues of personalized drug therapy in urology, issues of medical and biological differences (specifically the varying severity of pelvic organ ischemia) between certain patients as the reasons, while the clinical efficacy of LUTS drug treatment involving the use of OPC is individual. Further studies, including clinical trials, are needed to confirm the patterns identified and clarify their practical application.

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