ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

ORIGINAL STUDY

DOI: 10.23888/PAVLOVJ2018262222-228

АНГИОТЕНЗИНЫ В ЦЕНТРАЛЬНЫХ МЕХАНИЗМАХ РЕАЛИЗАЦИИ ПИТЬЕВОЙ ИНСТРУМЕНТАЛЬНОЙ АКТИВНОСТИ У КРЫС С РАЗЛИЧНЫМИ ПРОЯВЛЕНИЯМИ РИСКОВОГО ПОВЕДЕНИЯ

© Р.Я. Власенко[1], А.В. Котов[2]

ФГБОУ ВО Новгородский государственный университет имени Ярослава Мудрого, Великий Новгород, Россия (1)
ФГБУ Научно-исследовательский институт нормальной физиологии имени П.К. Анохина РАН, Москва, Россия (2)

Цель. Провести сравнительный анализ особенностей питьевой инструментальной активности у крыс с различными проявлениями рискового поведения до и после внутримозгового введения им равнорезультативных дипсогенных доз ангиотензинов. ***Материалы и методы.*** Работа была выполнена на 19 крысах-самцах породы Вистар массой 250-300 г. Все манипуляции с животными соответствовали международным этическим рекомендациям по проведению медико-биологических исследований с использованием животных. Под эфирным наркозом крыс предварительно скальпировали: удаляли мягкие ткани и надкостницу. Через трепанационное отверстие в боковой желудочек мозга крысы вводили канюлю. Длина каждой канюли составляла 8 мм, внутренний диаметр 0,8 мм. Канюли имели ограничитель на расстоянии 3,5 мм от вживляемого конца. Каждому животному вживляли одну канюлю в боковой желудочек мозга справа или слева, согласно координатам стереотаксического атласа для крыс (Л.Д. Пеллегрино с соавт., 1979) (AP= +1.0; L= 2; H= 2.5). Микроинъекции веществ в мозг выполняли ненаркотизированным животным с помощью микрошприца объемом 5 мкл («Hamilton», США). С целью внутрижелудочковых микроинъекций использовали ангиотензин-II, ангиотензин-III и [des-Asp1]-ангиотензин-I («Sigma», США). ***Результаты.*** В статье описаны механизмы реализации питьевой инструментальной активности у крыс с различными проявлениями рискового поведения. С позиций общей теории функциональных систем академика П.К. Анохина обсуждаются эффекты применения «равнорезультативных» доз ангиотензинов в инициации специфических паттернов питьевого поведения животных. Риск рассматривается как самостоятельный компонент системной организации целенаправленного поведения организма. Показано, что «интегральный паттерн индивидуального поведения» крыс избирательно модулируется ангиотензином-II и ангиотензином-III. Эта избирательность имеет узкую направленность и проявляется индивидуально, в зависимости от фоновой активности животных. ***Выводы.*** Ангиотензин-II и ангиотензин-III в зависимости от исходного уровня интенсивности инструментальной активности (с различными проявлениями рискового поведения) животных вовлекаются в инициацию полноценного «интегрального паттерна индивидуального питьевого поведения», либо участвуют в направленной модуляции сложного целенаправленного поведения, которая проявляется путем увеличения дипсогенного эффекта. Одновременно [des-Asp^1]-A-I не участвует в механизмах воспроизведения приобретенных питьевых инструментальных навыков, а индуцирует только механизмы инициации врожденных индивидуальных форм питьевого поведения.

Ключевые слова: *риск, ангиотензины, доминирующая мотивация, целенаправленное поведение.*

DOI: 10.23888/PAVLOVJ2018262222-228

ANGIOTENSINS IN THE CENTRAL MECHANISMS OF DRINKING INSTRUMENTAL ACTIVITY OF RATS WITH DIFFERENT MANIFESTATIONS OF RISK BEHAVIOR

R.Ya. Vlasenko[1], A.V. Kotov[2]

Novgorod State University named after Yaroslav the Wise,
Velikiy Novgorod, Russia (1)
Scientific Research Institute of Normal Physiology named after P.K. Anokhin,
Moscow, Russia (2)

Aim. To carry out a comparative analysis of characteristics of drinking instrumental activity in rats with different manifestation of risk behavior before and after intracerebral introduction of equally productive dipsogenic doses of angiotensins. ***Materials and Methods.*** The work was conducted on 19 Wistar male rats of 250-300 g mass. All manipulations with animals were performed in accordance with the international ethic recommendations on biomedical research with use of animals. All rats were preliminarily scalped under ether anesthesia with removal of soft tissues and periosteum. The cannulae were introduced into rat's brain through the trephine opening in the lateral ventricle. The length of each cannula was 8 mm, the internal diameter – 0.8 mm. All cannulae had a special restrictor at the distance of about 3.5 mm from the implantable end. Each animal was implanted one cannula into the lateral ventricle of the brain on the right or left side according to the coordinates of stereotaxic atlas for rats (L.D. Pellegrino at al., 1979) (AP = +1.0; L= 2; H= 2.5). Microinjections of substances were made into the brain of non-narcotized animals using a microsyringe of 5 μL volume («Hamilton», the USA). For intraventricular microinjections, angiotensin-II, angiotensin-III and [des – Asp1]-angiotensin-I («Sigma», the USA) were used. ***Results.*** In the article the mechanisms of realization of drinking instrumental activity in rats with different manifestations of risk behavior are described. In view of P.K. Anokhin's general theory of functional systems, the effects of application of «equally productive» doses of angiotensins on initiation of specific patterns of drinking behavior in rats are discussed. Risk is considered as an independent component of systemic organization of purposive behavior of an individual. It is shown that the «integral pattern of individual behavior» of rats is selectively modulated by angiotensin-II and angiotensin-III. This selectivity has a narrow focus and individual manifestations, depending on the background activity of the animals. ***Conclusion.*** Depending on the initial level of the intensity of instrumental activity of the animals (with different manifestations of risk behavior), angiotensin II and angiotensin III are involved into initiation of full-scale «integral pattern of individual drinking behavior» or participate in the directed modulation of complex purposive behavior manifested by enhancement of dipsogenic effect. At the same time, [des – Asp1]-angiotensin-I does not participate in the mechanisms of reproduction of the acquired drinking instrumental habits but induces only mechanisms of initiation of congenital individual forms of drinking behavior.

Keywords: *the risk, angiotensins, dominating motivation, purposeful behavior.*

According to an outstanding Russian physiologist academician P.K. Anokhin, a system-forming factor of a functional system of any level is a useful adaptive result of the activity which can be evaluated quantitatively [1]. The risk permits to predict the outcome of a situation, it is measurable [2] and performs several functions: stimu-lating, analytic, regulatory and protective [3,4]. A situation of uncertainty stimulates an individual to actions in

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the situation of choice, on the other hand – risk permits to evaluate usefulness (danger) of this choice. Trying to eliminate a risky situation, an individual makes a choice and realizes the aim in a behavioral act with subsequent emotional evaluation of the achieved result [5-7]. A.P. Algin [6] defines risk «…as an activity associated with overcoming of uncertainty in the situation of unavoidable choice in which it is possible to quantitatively and qualitatively evaluate the probabil-ity of achievement of the expected result, failure and deviation from the aim».

In our work a comparative analysis was carried out of individual-typological peculiarities of behavior of rats before and after intracerebral introduction of equally effective dipsogenic doses of angiotensins. A key criterion which served the basis of individual-typological classification of peculiarities of rats' behavior was the initial intensity of their behavior in the experiment determined by a quantity of instrumental acts terminated by intake of water.

Materials and Methods

The work was conducted on 19 male rats of Wistar line with 250-300 g mass. All manipulations with animals were performed in accordance with the international ethic recommendations on medico-biomedical research with use of animals. Scalping, implantation of cannula into the lateral ventricle were performed under ether anesthesia according to the coordinates of stereotaxic atlas for rats (L.D. Pellegrino at al., 1979) (AP = +1.0; L= 2; H= 2.5). Intraventricular microinjections of angiotensins («Sigma», the USA) were made to non-narcotized animals using a microsyringe of 5 μL volume («Hamilton», the USA).

Rats were taught instrumental skills on an automated setup – AS (A.V. Shvadchenko, A.P. Shcherbina et al., 1992) that permitted objective evaluation of successive fulfilment of stages of behavioral acts aimed at getting portions of water.

Training began with placing an animal into the start box where the rat occasionally found access to the treadbahn blocked by a mobile shutter. Then the rat per-formed a runway, he reached a rotating disk and had to turn it at a certain angle to move a water cup closer. After intake of water the rat was to return into the start box and again repeat purposeful act. The principal scheme of AS is given in Figure 1.

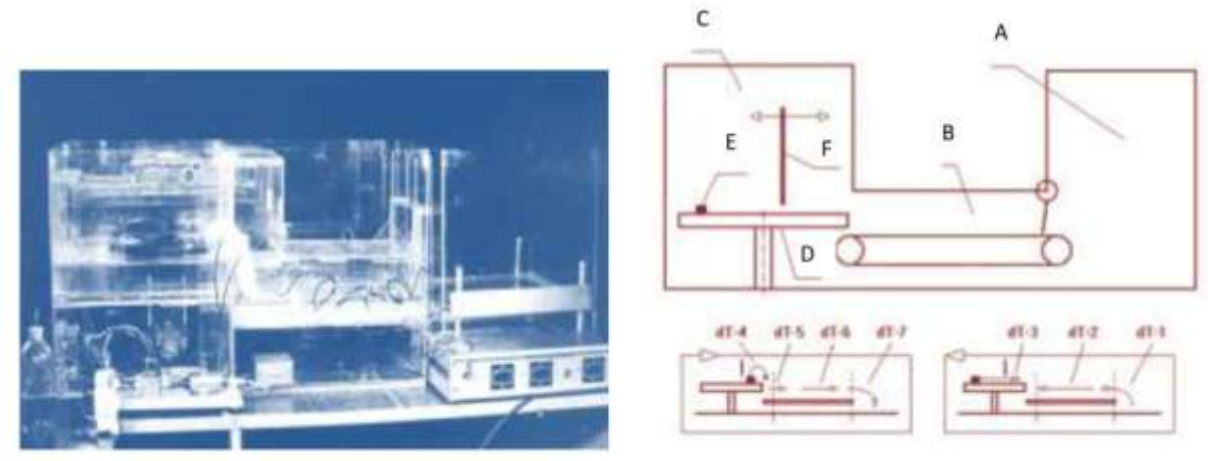

Fig. 1. General view and scheme of setup:
A – start box; B – «treadbahn» block; C – «manipulation» box;
D – rotating disk; E – water cup with a signal lamp; F – mobile curtain

DOI: 10.23888/PAVLOVJ2018262222-228

During training period rats were kept on a fixed supporting regime that is they were given water within 15 minutes once a day after daily manipulations in the set-up. Food was given without limitations. Temporal parameters of behavioral acts in rats were determined: dT-1 – latent period of coming onto the treadbahn; dT-2 – period from appearance on the treadbahn to taking the «manipulation» posture; dT-3 – time from start of «manipulation» to start of intake of water; dT-4 – time of intake of water; dT-5 – time from cessation of intake of water to withdrawal from «manipulation» posture; dT-6 – time of returning to the treadbahn; dT-7 – time of passage from the treadbahn to the start box. For evaluation of periods of the behavioral act (from dT-1 to dT-7) their absolute values were determined in sec. The time of testing of animals in AS was 10 minutes. Besides, there were also registered the number of pro-ductive instrumental acts, initiation of grooming acts and vertical upright postures, and the number of attempts to overcome obstacles on the way to water. The obtained data of behavioral experiments were processed using parametric Student's t-test for sampling with normal distribution.

After that animals with different manifestations of risk behavior receiving water and food ad libitum, were introduced doses of angiotensins equally effective in water intake: angiotensin-II(A-II) – 300 ng, angiotensin-III(A-III) – 350 ng and [des-Asp1] angiotensin-I ([des-Asp1]-A-I) – 400 ng («Sigma», the USA) into the lateral cerebral ventricles. «Equally-effective» doses of angiotensins that, being introduced into the lateral cerebral ventricles, initiated intake of equal amounts of water, were selected earlier in our research [8]. A solvent was normal saline solution (0.9 % NaCl), the volume of each microinjection was 3μL. Injection of saline with dissolved substances was made slowly within 15-20 sec.

Results and Discussion

By the results of experiment all rats were divided into 3 groups. The 1st group included animals (n=2, m=34 – number of runways in AS), whose behavior was initially inactive and was characterized by performing not more than 2 instrumental acts, by delay on the treadbahn (dT-7) when returning to the start box, and by a high level of species-specific activity (grooming, upright postures). After introduction of «equally-effective» dose of A-II the animals reproduced the same quantity of full-scale drinking acts, with reduction of the time of passage from the treadbahn to the start box ($dT\text{-}7^{-}$), prolongation of the time of intake of water (dT-4); the time of ex-it of the animals from the start box to treadbahn (dT-1) did not change. Taking into account peculiarities of the given individuals it can be stated that A-II not only reproduced the characteristic features of the instrumental pattern of drinking behavior, but also promoted fulfilment by the animals of the optimal algorithm of achievement of the useful result of their activity (intake of water, $p>0.05$ – compared to the initial level). According to the established strategy and effectiveness of the purposive drinking behavior, rats of the 1st group were classified as «non-risk-taking».

The 2nd group included rats (n=10, m=86 – the number of runways in AS) with moderate activity of drinking behavior (not more than 5 acts) which were classifies as «cautious» with «pragmatic» behavioral strategy. These animals demonstrated high values of time required for stages dT-4 and dT-7. Some rats (n=5, m=43 – the number of runways in AS) were made intracerebral microapplications of A-II. The dT-7 parameter reduced, that is, the time of passage from the treadbahn to the start box shortened in certain sessions, the time of intake of water increased (dT-4 – $p< 0.05$), the time of passage from the start box to the treadbahn remained unchanged (dT-1). In rats of the 2nd group the number of «references» to the empty water cup de-creased as well as the number of «references» to the shutter ($p<0,05$). In response to intracerebral introduction of A-II the grooming parameters unreliably increased ($p>0.05$ in comparison with that in the initial condition). Introduction of [des-Asp1]-A-I to the rats of this group was not accompanied by reproduction of the instrumental skill in them

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(duration of dT-1 period reliably increased as compared to the initial condition, $p<0.05$). Single non-effective runways towards the «manipulation» compartment were noted but they did not finish with manipulation with the disk and in-take of water. The number of grooming acts and upright postures reliably increased ($p<0.05$).

The 3d group included rats with high effectiveness (>5 acts). They (n=7, m=64 – the number of runways in AS) demonstrated the «beneficial» behavioral strategy – «risk-taking». The animals were under the «risk» of not to complete a large number of effective runways in the setup during the limited time of test. The longest period in these animals was the period of drinking act (dT-4, $p<0.05$), and all the rest additional activity appeared to be insignificant in comparison with other groups of animals. In these rats there were no «references» to the shutter and to the empty drinking cup in the initial condition, and the amount of «references» to the shutter strictly corresponded to the amount of productive acts in AS. They did not «fritter away» the energy to «empty activity» but pragmatically structured their purposive activity and achieved the useful result due to increase in the number of productive acts in AS. Changes in behavior in «risk-taking» rats after introduction of A-II were on the whole similar to those in the preceding group of animals. The time of consuming act (dT-4) did not change with microinjections, while dT-1 and dT-7 parameters increased. So, behavior of the animals was sort of rationalized. Animals to whom [des-Asp1]-A-I was injected, did not reproduce the drinking instrumental skill. The rats did not make a single attempt to overcome the shutter, their behavior was characterized by alternation of investigatory activity and grooming. Thus, introduction of [des-Asp1]-A-I suppressed realization of the «justified risk» strategy by probable destruction of probabilistic prediction of the result of activity [4,5,9]. However, after testing in AS, the dipsogenic effect of [des-Asp1]-A-I was manifested by additional drinking with free access to water, with the amount of consumed water corresponding to the effect of the equally effective dose.

Decision taking is an «intermediary, critical» and «highly condensed» process [1] that results from the afferent synthesis initiated by the dominating motivation [10]. Situation of uncertainty may be of «regular» or «occasional» character [6], in one case decision taking is associated with the conflict caused by the necessity to overcome a physical obstacle; in the other case – with the risk as a particular way of solution of the above mentioned conflict. Decision taking rids an organism of excessive «amount of degrees of freedom» and is accompanied by formation of specific «efferent excitations» having adaptive character [1,5,9] and reflected in the future result of behavior. An actual physiological task is evaluation and analysis of the functional parameter of risk-related behavior both in the process of decision taking and in the stage of realization of the behavioral act.

All components of the functional system of behavior are integrated and not absolutely independent and isolated. Dominating motivation, memory apparatus, decision taking are integrated, and risk is a specific component of behavior which appears in conditions of the uncertainty of achievement of the goal [5]. Risk is manifested as an independent characteristics of behavior of an individual, and changes in the biological functions associated with risk, are of adaptive character.

Conclusion

Depending on the initial level of the intensity of instrumental activity of animals, angiotensin-II stimulates reproduction of the full-scale «behavioral pattern» or participates in the directed modulation of complicated purposive behavior by its optimization in thirst. [des-Asp1]-angiotensin-I does not participate in mechanisms of reproduction of the instrumental skill, but only induces mechanisms of initiation of the inborn forms of behavior.

DOI: 10.23888/PAVLOVJ2018262222-228

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Дополнительная информация [Additional Info]

Источник финансирования. Бюджет ФГБОУ ВО Новгородский государственный университет им. Ярослава Мудрого. Бюджет ФГБУ Научно-исследовательский институт нормальной физиологии имени П.К. Анохина РАН. [**Financial support**. Budget of Novgorod State University named after Yaroslav the Wise. Budget of Scientific Research Institute of Normal Physiology named after P.K. Anokhin.]

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить, в связи с публикацией данной статьи. [**Conflict of interests**. The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

Участие авторов. Власенко Р.Я., Котов А.В. – концепция и дизайн исследования, сбор и обработка материала, статистическая обработка, написание текста, редактирование. [**Participation of authors.** R.Ya. Vlasenko, A.V. Kotov – concept and design of the study, acquisition and processing of the material, statistical processing, writing the text, editing.]

DOI: 10.23888/PAVLOVJ2018262222-228

Информация об авторах [Authors Info]

*__Власенко Роман Яковлевич__ – к.м.н., доц., кафедра нормальной физиологии, институт медицинского образования, ФГБОУ ВО Новгородский государственный университет им. Ярослава Мудрого, Великий Новгород, Россия. [**Roman Ya. Vlasenko** – MD, PhD, Associate Professor, Department of Normal Physiology, Institute of Medical Education, Novgorod State University named after Yaroslav the Wise, Velikiy Novgorod, Russia]
SPIN 9013-1219,
ORCID ID 0000-0002-7328-0520,
Researcher ID L-5352-2018.
E-mail: romex@mail.ru

Котов Александр Владимирович – д.м.н., профессор, заведующий лабораторией физиологии мотиваций, ФГБУ Научно-исследовательский институт нормальной физиологии имени П.К. Анохина РАН, Москва; заведующий кафедрой нормальной физиологии, институт медицинского образования, ФГБОУ ВО Новгородский государственный университет им. Ярослава Мудрого, Великий Новгород, Россия. [**Alexander V. Kotov –** MD, Grand PhD, Professor, Head of the Laboratory of Physiology of Motivation, Scientific Research Institute of Normal Physiology named after P.K. Anokhin, Moscow; Head of the Department of Normal Physiology, Institute of Medical Education, Novgorod State University named after Jaroslav the Wise, Velikiy Novgorod, Russia]
SPIN 2749-4037,
ORCID ID 0000-0002-1810-7741,
Researcher ID L-5375-2018.

Цитировать: Власенко Р. Я., Котов А.В. Ангиотензины в центральных механизмах реализации питьевой инструментальной активности у крыс с различными проявлениями рискового поведения // Российский медико-биологический вестник имени академика И.П. Павлова. 2018. Т.26, №2. С. 222-228. doi: 10.23888/PAVLOVJ2018262222-228.

To cite this article: Vlasenko RYa, Kotov AV. Angiotensins in the central mechanisms of drinking instrumental activity of rats with different manifestations of risk behavior. *I.P. Pavlov Medical Biological Herald.* 2018;26(2):222-8. doi: 10.23888/PAVLOVJ2018262222-228.

Поступила/Received: 17.11.2017
Принята в печать/Accepted: 31.05.2018