METHODOLOGICAL ASPECTS OF DRUG DEVELOPMENT AND PRECLINICAL RESEARCH IN THE INTERESTS OF ARTIC MEDICINE

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There is an inextricable link between exploration and development of the Arctic territories and emergence of associated problems of medical and biological nature. It is necessary to design and develop emergency care and prevention drugs and medical devices for use in the Arctic. This review presents an analysis of additional requirements for drugs intended for the Far North and compares methods of modeling extreme conditions in animals. We outline medical and biological problems of the region highlight key areas of Arctic pharmacology: choice of pharmaceutical form, use of cryoprotectants and design of adaptogens. The study mainly revolves around the search for information on modeling extreme environmental factors in animal experiments, as this is a key stage in preclinical studies of drugs for the Arctic medicine. We present the relevant directions of further work promoting the subject: development of the hypoxia and hypothermia assessment criteria, development of modeling methods employing large laboratory animals, improvement of the equipment used.

Keywords: hypoxia, hypothermia, photoperiodism, extreme environmental factors, animal research

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МЕТОДИЧЕСКИЕ АСПЕКТЫ РАЗРАБОТКИ И ДОКЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ В ИНТЕРЕСАХ АРКТИЧЕСКОЙ МЕДИЦИНЫ

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Освоение арктических территорий неразрывно связано с возникновением медико-биологических проблем. Необходима разработка медицинских изделий и лекарственных средств для профилактики или оказания неотложной помощи в условиях Арктики. В обзоре представлен анализ дополнительных требований к лекарственным препаратам, предназначенным для использования в условиях Крайнего Севера, и аналитическое сравнение методов моделирования экстремальных состояний у животных. Обозначены медико-биологические проблемы региона и акцентировано внимание на основных направлениях арктической фармакологии: выборе лекарственной формы, использовании криопротекторов и разработке адаптогенов. Основное внимание уделено поиску информации по моделированию экстремальных факторов окружающей среды в экспериментах на животных, так как это является ключевым звеном в доклинических исследованиях препаратов для арктической медицины. Показаны актуальные направления дальнейшей работы для развития данного направления: разработка критериев оценки состояния гипоксии и гипотермии, разработка методов моделирования на крупных лабораторных животных, совершенствование технического оснащения.

Ключевые слова: гипоксия, гипотермия, фотопериодизм, экстремальные факторы внешней среды, исследования на животных

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Almost 18% of the territory of the Russian Federation belongs to the Arctic region (AR). These are the lands from the Franz Josef Land to the Wrangel and Herald Islands, comprising about a third of the entire area of the Arctic shelf. The important transport corridors running through the AR condition the significance of this territory for the Russian Federation. Another reason for development of this region is production of hydrocarbons. With all the other factors considered, the Arctic is significant geopolitically on the global scale [1–4].

People permanently residing in the region back exploration and development of the AR: they power social and economic development, scientific research, infrastructural projects and environmental safety [3–5]. At the same time, development of the territories of the Far North is inextricably linked with problems of medical and physiological character that stem from the impact of severe natural and climatic conditions (cold, increased electromagnetic activity, radiation, specific photoperiodism etc) on the human body [4, 6–8]. Arctic medicine as a field of medical science was delineated with the aim of development of effective prevention and treatment measures; it studies the internal mechanisms of adaptation of the human body, seeks and describes specifics of the course of various diseases and develops methods for their treatment [9].

This review made use of the PubMed and Google Scholar resources. We gave preference to papers published over the past 10 years and indexed in the Scopus and Web of Science databases. The key words cited above were used in the search for publications.

The purpose of this review is to present an analysis of additional requirements for drugs intended for the Far North and compare the methods of modeling extreme conditions in animals.

Medical and biological problems of the Arctic region

Climatic and geographic, psychological and physiological factors peculiar to the AR have a significant impact on life of people. They trigger involvement of all physiological reserves of the body and a complex restructuring of the homeostatic systems [10–12].

Extremely low ambient temperatures exacerbate the need for heating, the body produces more heat at the expense of efficiency of physical work, which goes down [13]. Metabolism of a human being changes: the need for proteins and fats, fat-soluble vitamins (A, D, E etc) increases [6, 13]. This translates into special nutrition and work/rest requirements [14].

In addition, conditions of the AR support development of tissue hypoxia, which can have various physicochemical or physiological causes (changes in the structure of membranes of erythrocytes that deliver oxygen to tissues etc) [14–15]. The increased need for oxygen on the part of tissues affects the respiratory system and triggers adaptive changes aimed at improvement of gas exchange, i.e., growth of the alveolar surface of the lungs and volume of the pulmonary capillaries [14].

The influence of the Arctic's low temperatures and rarefied atmosphere should be considered in combination, since these two factors can be mutually potentiating [15]. In particular, cold causes vasoconstriction and decreases the intensity of blood flow in general and to the skin in particular, which results in local cooling of hands and feet, face and upper respiratory tract, a process that negatively affects physical performance and changes the functions of external respiration [16–17]. In addition, combined with cold stress, hypoxia contributes to the development of ischemic changes in cardiomyocytes, thus affecting the cardiovascular system [15].

Photoperiodism is another factor that, similarly to exposure to low temperatures, significantly affects physiological state of a person in the AR [18–19]. Almost all cellular functions and physiological systems of the body are under circadian control, a "mechanism" that keeps body's activity at the optimal level, supports energy conservation and maintenance of internal homeostasis [20]. The circadian rhythm (CR) is driven from within, but it is synchronized with external stimuli, including, in the first place, light of a certain portion of the spectrum and intensity [21–22]. There is a pronounced seasonal asymmetry of light availability and insufficient ultraviolet radiation in the polar zone. Combined with the effects of the cold, stress associated with the light alters functioning of the body's hormonal systems [21, 23]. A mismatch between the CR and external signals can lead to the development of metabolic, immune and mental diseases, as well as undermine the effectiveness of wound healing, body detoxification etc [24]. A person may start suffering from desynchronosis, which manifests in deterioration of physical and mental performance, sleep disturbances and unpredictability of human behavior [10, 13, 25].

In the context of studying the AR-associated factors, changes in the body's CR should be considered in conjunction with hypothermia. Body temperature rises during the day and goes down at night, which ensures the optimal course of physiological processes. Various diseases and specifics of their course are also associated with body temperature fluctuations, e.g., high temperature typically indicates a significant systemic inflammatory response [26].

In the AR, the light as direct solar radiation and as rays reflected from the snow is an aggressive factor. The small angle of incidence typical for the region reinforces the effect of light in the visible and ultraviolet spectra. Lack of prevention measures and protection equipment leads to burns of the eye's conjunctiva and cornea, a condition called snow blindness [27].

Another medical and biological problem peculiar to the AR is the wide spread of infectious diseases, including those of emerging from the wilderness in a given location (anthrax, etc.). The two key reasons behind this problem are the large hosts blood-sucking dipterans in the summer and crowded accommodation conditions with people spending most of their time in an artificial environment [6, 28]. Poor water quality also plays a significant role. Meltwater contains heavy metals, organic pollutants and various microorganisms. Consumed for a long period of time, such water disrupts the water-salt exchange in the body, contributes to the leaching of salts and slows down tissue recovery in case of injuries [29].

The diseases that are more common in the AR and less spread in the moderate climate belt deserve a special mention [1]. General hypothermia and the resulting tissue hypoxia and ischemia-reperfusion syndrome hinder healing of various injuries of the skin and soft tissues, including frostbite. Hypothermia aggravates the injuries by disrupting plasma coagulation and platelet function, suppressing the immune response and increasing the risk of sepsis. Damage to local vessels worsens hypoxia in the injured tissues, which prevents collagen synthesis and angiogenesis and slows down tissue regeneration significantly. As a result, surgical intervention as per the standard protocols may be delayed, with such a delay increasing the risk of death of a seriously injured patient [30–31].

Extreme climatic conditions, low population density, remoteness and inaccessibility of the areas comprising the region affect the setup of medical care (MC) systems, including those involved in rescue of people injured in emergency situations [30]. The specifics of provision of MC is also a reason behind the need for development of the new methods of treatment.

Cold climate makes most medical manipulations impossible. Therefore, design of modern equipment, medical devices/ items (MDI) and drugs suitable for use in the AR is strategically important, with resistance to extreme low temperatures being one of the key requirements and resistance to humidity and radiation, wind loads and precipitation, as well as stability under multiple cycles of exposure to adverse factors being additional requirements.

The use of drugs and MDI for treatment of diseases in the AR can be divided into three categories. The first group includes drugs necessary for first aid when condition of the patient is life-threatening. The drugs (and MDI) of this group relieve pain, stop massive bleeding and prevent asphyxia; they are used outdoors under the most aggressive conditions. The second group can be considered comprised of drugs intended for use in a limited space, e.g., a first-aid post. In this case, the impact of winds, precipitation and low temperature is minimal, and it mainly manifests during transportation. In addition to first-aid drugs, preventive medicines can be also allocated to this group. The third group includes drugs, MDI and, potentially, cell products used in an in-patient hospital outside the AR. The selection criteria for this group are conditioned by the combined effect of the factors of the Far North on the body, which translates into complication of the pathogenesis of diseases.

Prevention and treatment drugs

Prevention and first aid in the North require a certain set of drugs and MDI. The following groups of essential drugs can be distinguished: cardiovascular drugs, analgesics and antispasmodics, antibiotics and antiviral drugs, drugs for treatment of respiratory diseases and frostbite, adaptagens adaptogens and preventive drugs (e.g., for eye protection), vitamins.

There is a number of limiting factors to be taken into account when selecting drugs for the AR. Many drugs cannot be frozen. Liquid drugs are designed primarily for use at abovezero ambient temperatures. The stability of a drug can suffer during transportation over hundreds of kilometers, which is often done in vehicles not equipped specifically for the purpose. Low temperatures, high humidity, bright lighting and mechanical shocks, as well as uncontrolled freeze-thaw cycles directly affect the quality of the drug. It is also necessary to factor in the possible reinforcement of adverse effects the drug may have on the body.

From the usability point of view, hard and soft liquid drugs are the most convenient. Low temperatures make drugs more fragile and violate the integrity of the film shell of pills and capsules. Various band aids and dressings, if exposed to low temperatures, can lose their adhesive and functional properties. If the patient needs care at the place of accident, it becomes increasingly hard to apply them because of the many layers of clothing. Also, it may be difficult to use powders and granules to make liquid preparations.

For first aid, injectable drugs (e.g., painkillers) are most effective. They are less resistant to repeated freeze-thaw cycles. Cryoprotectants (alcohols, polymeric compounds etc) can be used to reduce the defrosting time and/or prevent freezing, as well as to protect the active component from degradation [32]. A cryoprotectant cannot be toxic, it should not accumulate in the body and be quickly eliminable in order to prevent the development of side effects [33]. Another important requirement for such protection is lack of any negative influence on the active agent.

Propylene glycol, a polyhydric alcohol completely metabolized by the body, is one of the promising cryoprotectants [33–34]. Today, it is used as an additive to diazepam (200 mg of propylene glycol per 1 ml of the drug, which is 19% of the volume) and other drugs for intramuscular or intravenous administration. Preliminary studies have shown that propylene glycol added to the anesthetic at a concentration below 40% decreases the freezing point to values below minus 25 °C while not affecting efficacy of the active ingredient in any way (unpublished data).

Another direction AR medicine takes in addition to the path of improvement of the already existing drugs is design of adaptogens, biologically active substances of plant or animal origin intended to enable adaptation of the body (its cold resistance and cognitive capabilities in particular) to extreme conditions and reinforce its physical capacity. Design of adaptogens is a difficult task: there is no specific pharmacological target and it is necessary to produce a complex effect on various organs and systems. Another problem with adaptogens is the unpredictable intensity of their effect, which differs depending on who made the drug [35].

Only a small number of drugs and MDI are produced specifically for use in the Arctic. The reason behind this situation is the set of additional requirements for such products that condition their use when there is an impact from a combination of external factors.

Simulation of extreme conditions in animal experiments

Climatic testing rigs and subsequent application of the advanced physicochemical and biochemical methods can enable *in vitro* assessment of stability of the drugs and MDI after exposure to aggressive factors inherent in the Far North.

There are rigid limitations for *in vivo* studies. It is necessary to develop and implement models that allow assessing the functions of cardiovascular, nervous, endocrine and immune systems of the body, as well as external respiration. Such studies could support the methods of regulation of adaptive capabilities of a person in the conditions of the AR [4, 36].

Hypoxia is a factor that significantly handicaps performance. It was established experimentally that a gas mixture with the content of oxygen at 10% alters the pulmonary ventilation pattern from the first minutes it is breathed, with hyperventilation and increased respiratory minute volume being the compensatory mechanisms to manifest earliest [37]. Therefore, investigation of the body's adaptive capabilities should start with experiments involving hypoxic hypoxia associated with a change in the barometric pressure of the inhaled air or a less oxygen-rich breathing mixture [38]. Rodents are the main experimental animals in this context; they are placed in hermetic chambers of various sizes with controlled level of rarefaction of the atmosphere or gas mixture. However, there is no single methodological approach to assessment of severity of the induced hypoxia that would apply to all the various models used by researchers. When used to evaluate the action of a drug on the body, hypoxic hypoxia tests only confirm the antihypoxic effect of the drug and describe its intensity, but report no specific level thereof [38].

The range of variations is greater for simulation of hypothermia in models. A body's temperature can be decreased by cooling the air in the hermetic chamber, by immersion in cold water [39–40], by wrapping the body of an immobilized animal in ice or by placing it on a cold surface [41]. These methods can also be combined. The specific conditions of the experiment define how the decrease of the animal's body temperature and specific features of the model affect experimental results (Table 1).

Physiological features of the rodents should be factored in when aligning body temperatures and states, however, there is no single classification developed for this purpose. Some researchers consider body temperature below 37 °C to be low and 35 °C — critical [46], some take into account

Table 1. Methods of modeling hypothermia in rodents

Animal	Method	t_{ext}, °C	τ	N	t_{rect}, °C	Additional factors	Reference
Mice	contact (metallic plate)	18	8 h	1	33	anesthesia	42
Rats	cold water	12–14	10–20 min	1	34–35	immobilization	41
	hermetic chamber	4–6	160 min	1	36–38	immobilization, humidity 75–80%	
Rats	hermetic chamber	1–2	3.5–4 h	1	14–18	hypoxia (chamber 5 L)	43
Rats	hermetic chamber	2–6	2 days	10	36–37	hypoxia (15% O_2)	44
Rats	hermetic chamber	minus 25	3–9 h	1	30	no	45
Rats	hermetic chamber	4–6	14 days	groups	33	hypoxia (30–50 mg/kg $NaNO_2$), humidity 75–80%, stress factors (light, sound, food restriction)	23

Note: t_{ext} is ambient temperature; τ is the time of keeping under simulated extreme conditions; *N* is the number of animals kept simultaneously under simulated conditions (in one cage, if a hermetic chambers was used; group — the exact number of animals in a cage is not given); t_{rect} is the rectal temperature of the animals at the end of the keeping period or a limiting value the reaching of which triggered removal of the animal removed from simulated conditions; additional factors list the conditions created while keeping animals in simulated extreme conditions, like immobilization of animals in a plastic case.

the range of moderate hypothermia, 32–35 °C [23]. Thus, modeling hypothermia requires development of the uniform methodological recommendations based on the reference data describing physiological characteristics of the selected animals.

Despite the fact that using cold air to lower the animal's temperature to the desired level is a time-intensive approach, hypothermia is mainly simulated in hermetic chambers (Table 1) because they allow combining this state with other factors, such as hypoxia [15]. High humidity created in the chamber enhances the effect of cold on the animals. One paper reports using light as an additional stress factor.

As mentioned above, same as hypothermia and hypoxia, photoperiodism has a significant effect on living organisms in the AR. Circadian rhythms should be factored in when calculating dosing schedules and evaluating the efficacy of drugs and measuring their blood levels. It has also been confirmed that the acute symptoms of many diseases and conditions manifest at certain times of the day (myocardial infarction, rheumatoid arthritis). Thus, circadian regulation of the molecular processes can affect condition of the patient and results of the therapy [20].

There are three ways of changing the CR in experimental animals: with light, food and temperature. Ambient temperature has a weak synchronizing effect, since animals have internal mechanisms that ensure temperature compensation. It is possible to "reset" the CR with a non-light stimulus. Time-restricted feeding is a popular approach when the goal is to study the CR proper, however, if the feeding period is less than 6 hours, animals cannot eat as much food as they do *ad libitum* [44]. This additional stressor must be taken into account in the experiment.

In our opinion, light is the preferable stress factor for experiments designed to simulate conditions of the AR. As a rule, standard animal keeping conditions imply a 12-hour day and a 12-hour night. Increasing the daylight hours to 22 hours or reducing their duration to 2 hours results in disruption of the CR of animals. Rodents, for example, are night animals, so a longer day translates into a stress for them.

Using the published data, we compared all the available methods and assessed the possibility of combining them (Table 2). Most of the methods are described in single publications only, which highlights one of the main problems faced when compiling guidelines for preclinical studies of drugs intended for the AR: insufficient number of experimental studies. To date, the only document is the antihypoxic drugs activity investigation guidelines [38], which describe modeling of various hypoxic conditions in animals. Unfortunately, we have not found similar guidelines for hypothermia or photoperiodism.

Taking into account the advantages and disadvantages of the methods and the possibility of combining them, the following recommendations for modeling the Arctic factors in preclinical small animal model studies can be formulated. Such research requires keeping the rodents for a long time, therefore, to create hypothermia, it is necessary to use a hermetic chamber. The recommended temperature is 2 through 6 °C. The maximum number of animals in a cage is five, because when the group is larger, the animals huddle together and warm each other. The preferred approach is to keep one animal per cage, but that is not always possible. The humidity in the chamber can be increased in order to amplify the effect of cold. If the study

Table 2. Simulation of extreme conditions of the Arctic

Factor	Method	Advantages	Flaws	Possible combinations with other stressors	Possibility of assessment of physical or behavioral activity*	Experiment duration
Hypoxia	Use of a hermetic chamber	Applicable to a group of animals; use does not require additional skills	Mainly for small laboratory animals; restriction of manipulations with animals is necessary; the parameters are controlled in different points of the chamber	Hypothermia (hermetic chamber, cold water), photoperiodism (light, food)	Tests that could be performed inside the chamber or other short-term (up to 5 minutes) tests outside the chamber	Several days or more
	Inhalation (mask)	Precise composition of the inhaled air	Mainly for large laboratory animals; wear training required	Hypothermia (all), photoperiodism (light)	Depending on the test	Several hours
	Hemic (IV introduction of hemoglobin oxidizer)	Creating a certain level of hypoxia	It is necessary to select concentration and pattern of administration for each animal species due to possible individual intolerance	Hypothermia (all), photoperiodism (light, food)	Carrying out any tests (theoretically)	Several days or more
Hypothermia	Use of a hermetic chamber	Applicable to a group of animals; use does not require additional skills	Mainly for small laboratory animals; the parameters are controlled in different points of the chamber	Hypoxia (all), photoperiodism (light, food)	Tests that could be performed inside the chamber or other short-term (up to 5 minutes) tests outside the chamber	Several days or more
	Immersion in cold water	Rapid achievement of the required body temperature, possibility to combine with physical activity (swimming, swimming with a load)	Higher difference between cold-resistant and cold-sensitive animals	Hypoxia (hermetic chamber, hemic)	Swimming or taking the animal out of the water for a short period of time for other tests	Several hours
	Contact (cold surface, ice)	Convenience of control over physiological parameters when the body temperature drops	Requires anesthesia for each animal individually	Hypoxia (mask, hemic)	Impossible	Several hours

Note: * — indicates the possibility of conducting tests while maintaining the impact of stress factors on the body.

does not include behavioral or long-term experiments (more than 5 minutes) involving removal of the animals from the chamber, it is preferable to induce hypoxia through inhalation, by maintaining a given oxygen level in the hermetic chamber. In case the experimental phase of the study includes periodic tests or repeated daily manipulations, it is advisable to use smaller hermetic chambers containing 2–3 cages with several animals, or individual hermetic chambers, or induce hemic hypoxia. This is necessary to reduce the time spent by animals outside hypoxia and the time needed to restore the required level of oxygen in the air if hermetic chambers are used.

Lack of guidelines and standardized equipment, as well as insufficient amount of practical research, necessitate preliminary experiments with a specific rig before each study. Firstly, this approach allows assessing the effect of hypoxia and hypothermia on the animal's body in each case (with body temperature taken at short intervals, blood sampling etc.) and ensures significant reduction of the number of manipulations during the main experiment while maintaining the value of the resulting information; for example, in a preliminary experiment, temperature of the animals can be measured (rectally) every 6–12 hours for several days, and during the main experiment, the frequency of this operation can be reduced to once a day, with the obtained values compared with the data registered during the preliminary study. Secondly, a preliminary experiment allows identifying animals that are resistant or sensitive to stressful conditions, which is important. Studies [23, 41] have shown that external stress factors affect animals differently: about 10–20% of rats in the experiment proved to be resistant thereto as their body temperature decreased much more slowly than in other rodents. Thus, this approach, depending on the experimental conditions, enables preliminary selection and formation of experimental groups with equal numbers of sensitive and resistant animals. The published data allows a conclusion that identification of resistant animals and determination of the key parameters of the animals' state can last 2–3 days, while the main phase of the experiment can take up to two weeks. It should also be noted that such a two-phase approach implies using the same animals, which necessitates special attention from the bioethical commission to the procedures implemented during the preliminary test. It is extremely important to minimize the negative effect the first phase has on the animals' condition and establish the optimal period between the preliminary and main experiments to ensure their full recovery.

The most popular animal models are rats. It is difficult to plan an experiment and create AR conditions for larger species: their resistance to hypoxia is lower than that of rodents [38]. In this connection, one of the urgent tasks is to scale up existing or develop new methods of modeling extreme environmental conditions that would be suitable for other (larger) laboratory animals.

Criteria of assessment of severity of factors is another area that lacks the required sufficiency. There are physiological and biochemical hypoxia severity assessment criteria described for small animal models [38], but there is nothing of the kind for their larger counterparts. As for hypothermia, it is typically evaluated by rectal temperature alone, and its degree is established based on the literature data that the researcher prefers. There is, however, a consistency peculiar to these data, although not a complete one, which enables comparison of the results obtained. Addition of photoperiodism to the list of factors behind the extreme conditions simulated necessitates development of the main criteria of assessment of light-associated stress in animals, as reflected by, for example, temperature and/or cortisol and melatonin levels [20].

As Table 1 shows, hermetic chambers are a common tool used for modeling the AR conditions. In this connection, a technical problem should be noted: lack of specialized equipment translates into custom rigs designed and made for a given experiment. This problem is important because reproducibility of the results largely depends on standardization of the equipment. The chambers used should maintain values of the parameters (temperature, oxygen level, etc.) uniformly throughout the entire volume of the chamber. A separate task is the selection of the optimal methods of registration of vital signs of the animals since opening the hermetic chamber alters the conditions therein and entails the need for restoration of the required parameter values. Technological aspects should be considered in development of the AR conditions simulation methods designed for other animal species.

There are many factors (age, gender, etc) that shape the body's resistance to extreme influences and diseases. For the most part, simulations of extreme conditions employ healthy animals, but in clinical practice, extreme factors have a greater effect on people with chronic diseases. Therefore, to make extrapolation objective, a group of researchers has suggested [47] working with animals that have a persistent pathological condition, for example, an unpaired variation of the organ that is typically paired. We have not taken into account that study when comparing methods of modeling hypothermia in rodents because it offers insufficient data on the characteristics of the simulated conditions in animals. However, the report confirms that viability of the animals under extreme conditions after nephrectomy decreases, and shows the possibility of implementing this approach in the experiments designed to assess action of a drug.

In connection, modeling of pathological states is an important aspect of preclinical research in the interests of the Arctic medicine. Residents of the AR have their own characteristic diseases, the most common of which is frostbite. It is defined as a complex of pathological changes occurring as a result of local and general cooling of the body. There are several experimental models [48] used in the investigations of the mechanisms of condition development and treatment, as well as assessment of drugs and therapeutic methods. It is possible to induce different degrees of frostbite, but reproducibility for some of them is low. Moreover, in most cases the damaged parts are the limbs, and in the animal experiments it is the trunk that is injured. Therefore, it is necessary to further develop the models in order to open the possibility of combining cryoinjury with other effects and ensure reproducibility of wound characteristics [48–49].

We have found no studies simulating other diseases that may be complicated by the extreme environment factors peculiar to the Arctic. This is another problem in further preclinical studies, since the course of a pathological process without treatment under extreme conditions will require additional modeling and investigation. Assessment of efficacy of a drug will include comparison with its action on animals kept under standard conditions. We have designed models of a lacerated wound [44], frostbite and chemical burn under conditions simulating those of the AR. The latter mice model has shown that inflicting a third-degree burn to animals kept in a climate chamber for a day takes less time compared to animals that were not placed in a hermetic chamber (unpublished data). A possible reason therefor is the significant drop of skin temperature compared to rectal temperature, since temperature of back and limbs of the animals differs from temperature of their rectum by about 0.5 and 6 °C [46]. Similar nuances can also arise in other models of diseases, primarily those related to the skin, musculoskeletal system and respiratory system.

CONCLUSION

Despite the accumulated knowledge and experience, there is no tested and certified set of methods for assessment of impact of cold on the body of an animal [37]. This is also true for *in vivo* investigations of hypoxic conditions. The role of the photoperiod in extreme conditions is often overlooked. In general, the complexity and multitude of factors accounted for in the designs of such experiments translate into lack of a unified approach to them. Yet, hypoxia and hypothermia experiments under controlled conditions are necessary not only for pharmacological but also for physiological studies [37], which, in turn, requires development of a theoretical and regulatory framework, as well as methodological recommendations that, combined, would enable development of reproducible models.

A matter of special importance in design of drugs for the Arctic is their optimal form, improvement of properties of injectable drugs with the help of cryoprotectants. Another topical area that should be highlighted is development of adaptogens.

In our opinion, the most difficult task is modeling the extreme conditions of the AR in animal experiments, with hypothermia, hypoxia and photoperiodism being the key factors. Today, it is possible to compile recommendations for conducting such studies on small laboratory animals, but there are significant gaps in understanding what methods can be used to recreate the impact of the Arctic factors in a large animal model experiment. It is necessary to develop criteria of evaluation of all the listed conditions and standardize the technical base.

A separate area of research is modeling of pathological conditions (diseases) that may be complicated by the effects of aggressive factors peculiar to the AR. Developments in this area can stimulate design of the new, more effective drugs that will be usable not only in the Far North.

There is a positive trend that should be mentioned: every year, there is more and more data published on the capabilities of organisms to adapt to the extreme conditions of the AR. The techniques and hermetic chambers being developed for *in vivo* experiments may also be applicable in other areas, for example, in development of treatment regimens for victims of catastrophes associated with rapid cooling, such as submarine accidents. In terms of the extreme natural factors, these studies have much in common with investigations revolving around the highlands, where the leading role is also played by the oxygen partial pressure drop that stimulates development of tissue hypoxia. Low air temperature with significant daily fluctuations and strong winds increase the risk of respiratory diseases, frostbite and chills [50].

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