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Article

Astrotoxicology

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Abstract: After astrochemistry and astrobiology, astrotoxicology is a further subfield of astroscience. Astrotoxicology is an interdisciplinary science that combines physics, biology, chemistry, astronomy, medicine and toxicology. Unlike toxicology on Earth, astrotoxicology in space must take into account the specific features of extreme conditions such as gravity, radiation, temperature or pressure and also consider the distinctions of extreme conditions on other celestial bodies. The field of action of astrotoxicology is, therefore, the influence of lower gravity on the toxicological characteristics of substances in the human body, the special dangers caused by increased radiation in space and on other planets and the special chemical changes caused by the extreme conditions in space on substances and the toxicological consequences associated with them. Despite growing space research, there are so far only a few pharmacokinetic, pharmacodynamic or toxicological investigations under conditions of microgravity and knowledge of toxicology under the extreme conditions in space in particular. Future studies will be the beginning of astrotoxicology, a previously unknown branch of toxicology.

Keywords: astrotoxicology, astrobiology, astrochemistry, mars, manned space flight, micro-gravitation, radiation

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1. Introduction

Astrochemistry looks at chemistry in the universe. A sub-area is cosmochemistry, which carries out chemical research on the elements in the solar system, such as planets and meteorites. Without a man-made vehicle having ever lifted off from the surface of the earth, spectroscopic analysis of the sun could already be carried out in the 17th century. In 1868, Lockyer was thus able to spectroscopically discover helium in the sun [1]. The element was named after the Greek name for sun Helios. In the 1930s, molecules were first identified in interstellar space. In 2009, the simplest amino acid glycine was found [2]. In 2012, the sugar molecule glycol aldehyde could have been detected near the star IRAS 16293-2422, at a distance of 400 light-years [3]. It can be assumed that complex organic molecules already form before the formation of planets. Basically, the field of astrobiology is a further scientific development of astrochemistry. Astrobiology searches for traces of chemical evolution and for evidence of former or still existing life in our solar system. Other topics are field studies on the origin of life on Earth and the adaptation of life to very hostile places such as Antarctica.

The term astrobiology was first used in the 1930s by Ary J. Sternfeld (1905-1980) [4] and 1941 by L.J. Lafleur [5]. Until the 1960s, the term astrobiology was subject to mockery due to the small amount of data available. Thus, in 1964, G. G. Simpson said that astrobiology first of all had to prove its existence as field of research [6]. Another field of research which is now being created by manned space flight is astrotoxicology. In 2003, the term astrotoxicology was mentioned for the first and only time in a scientific publication. In an astrobiological paper Aller et al. wrote "Toxicology is the branch of pharmacology that deals with nature, effects, detection and treatment of poisons. Like terrestrial biology with its counterpart of astrobiology, so does toxicology with astrotoxicology." [7]. There were no further explanations on astrotoxicology. However, astrotoxicology deals with toxicology under reduced gravity, the special dangers of increased radiation for humans and matter in space, and toxicological phenomena that are likely under extreme space conditions due to special chemistry. Astrotoxicology is an interdisciplinary science that combines physics, biology, chemistry, astronomy, medicine and toxicology as shown in Figure 1.

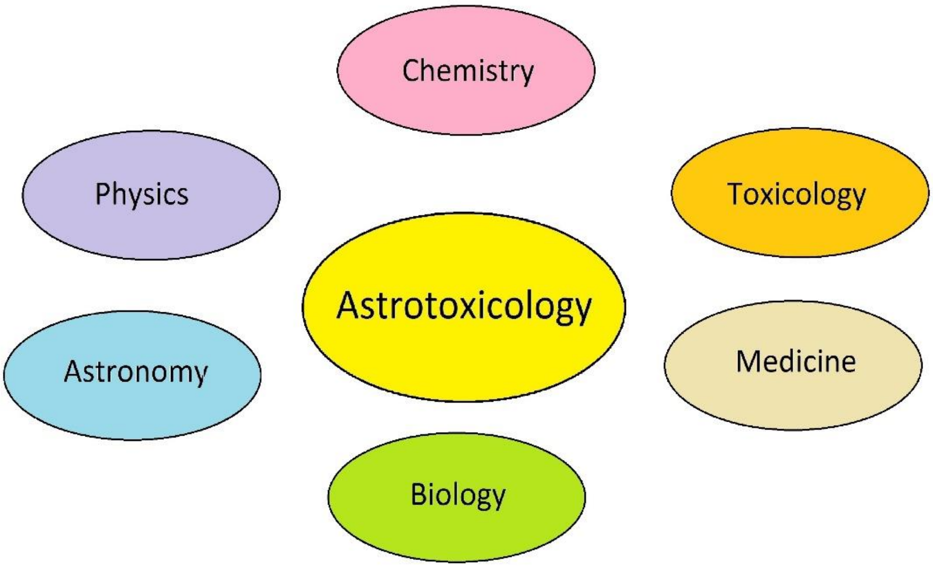

Figure 1. The interdiciplinary science of astrotoxicology

Unlike toxicology on Earth, astrotoxicology must take into account the particularities of extremeconditions such as gravity, radiation, temperature or pressure in space and on other celestial bodies. The field of activity of astrotoxicology includes studies in the following areas:

1. Influence of lower gravity on the toxicological characteristics of substances in the human body

2. Dangers to man and matter from increased radiation in space

3. Toxicological changes caused by extreme conditions in space

2. Influence of zero gravity on the human body

By December 31, 2018, there were only 562 people who had ever been in space, 24 had left the Earth's gravitational field towards the Moon, and 12 had actually entered the Moon. In human history there have never been more than 13 people been in space at the same time. On the whole, all astronauts of all times have gathered only 142 years of astronaut experience. In fact, there have been fewer Nobel Prize winners, Olympic champions or dollar billionaires in history than people in space. The effects of microgravity on the human body are manifold. It leads to bone and muscle degradation, the sense of smell is impaired and because of the lack of gravity, the leg veins press volume into the upper half of the body. The spine expands, so that the astronaut appears to be about 8 cm taller. Lack of sleep and fatigue are among the most common complaints during a space flight. The constant day-night changes at the ISS and the great amount of noises from fans and on-board electronics reduce the quality of sleep, so that most astronauts take sleeping pills. In the beginning about half of the astronauts feel nauseous. The amount of cytochrome P-450 and the activity of various dependent enzymes decreases, which affects the pharmacokinetic and pharmacodynamic properties of drugs [8]. Approximately half of the astronauts suffer from the so-called space sickness which is mainly characterized by nausea, vomiting, headaches and loss of appetite due to an irritation of the sense of balance in microgravity. In addition, skin rashes that are in need of treatment are widely spread. This may be caused by the reduced body hygiene due to low water supplies, a weakened immune system and the frequent use of disinfectants [9]. The experience of a longer impact of low gravity (1/6 of the Earth's gravitational force as on the Moon) or zero gravity (more precisely microgravity, on the ISS there is about 1/1000 of the Earth's gravitational force) in orbit has thus been an extremely rare experience for humans as shown in Table 1.

Table 1. Space experience of mankind until 2018

Persons	Event
562	In space
213	Space walk in the orbit of the Earth
24	Flight to the moon
12	Walk on the moon
3	Space walk in moon orbit

3. Pharmacokinetics and Pharmacodynamics in Real and Simulated Microgravity

So far, the field of astrotoxicology has not found its way into current toxicological literature. All long-term studies under microgravity could currently only be carried out during space flights or on the International Space Station ISS. The cost of a ticket for a ten-day stay there amounts to about 50 million Euros. Therefore, not surprisingly, toxicological examinations under microgravity are practically non-existent. Also pharmacodynamics in space, i.e. the influence of active substances on the organism under conditions of microgravity (weightlessness), is largely unexplored. Until 2017, there were only three studies on pharmacokinetics during space flights [9]. One study tested the absorption of paracetamol where two pills of 325 mg active substance each were examined by five astronauts on three different missions with the space shuttle. The active substance was increasingly absorbed in the first two days, while the intake decreased after four days [10]. Table 2 shows frequently used medicines in space.

Table 2. Medicines frequently used in space [11]

Drug	Indication	Efficacy
Zaleplon, Zolpidem, Melatonin	Sleep-through disorders	Moderate to very effective
Ibuprofen, Paracetamol	Pain	Moderate to very effective
Glucocorticoids, Fungicides, Antihistamines	Skin rash	Moderate to very effective
Promethazine	Space-Adaption-Syndrome	Very effective (prophylaxis)

A different study investigated the pharmacokinetics of 0.4 mg scopolamine with 5 mg dextroamphetamine at 12 astronauts [12]. In this study, the test participants showed large deviations. The latest study tested the pharmacokinetic properties of paracetamol in two dosage forms under long-term conditions. Five astronauts took 500 mg active substance compared to a control group on the ground. Bioavailability increased in microgravity, absorption time decreased, half-value time and residence time of the active substance increased [13]. The difficulty to obtain data under space conditions requires more easily available methods to simulate zero gravity conditions. Soil-based studies with simulated microgravity offer an inexpensive alternative. For that matter, the test subjects rest in bed with the legs at an angle of 6° upwards. As a result, the blood flow direction is more towards the head, which is a good simulation of the conditions under microgravity. During the experiments, all activities such as eating, drinking and washing must be performed in a lying position with at least one shoulder always in contact with the bed. The strenuous efforts for the test persons to take part in this three-month's test with this experimental set-up is compensated with an expense allowance of 16,000 Euros [14]. Experiments with simulated absence of gravity showed an increased absorption of paracetamol, while the time to maximum concentration decreased [15]. A different study investigated the pharmacokinetic behaviour of promethazine. In the process, a 30 % increase in bioavailability was found. A possible cause for this is the prolonged contact time with the intestinal wall of the test subjects in this particular lying position [16]. Furthermore, a faster onset of action of ibuprofen with high dissolution and absorption rates was observed [17]. A further analysis showed that no dose adjustment is necessary when using the active substance propofol [18]. In practice, drug doses in space are so far the same as on Earth.

4. Radiation as a Health Hazard

Significantly higher cosmic rays during a stay in space pose a threat. The biological danger results from the high-energy radiation, which has an ionizing effect. The amount of energy as such is low. The amount of energy absorbed is called the equivalent dose. In former times, rem was the relevant unit but meanwhile the equivalent dose is indicated in Sievert (Sv). 1 Sv corresponds to 100 rem. At a dose of 4 Sv, which corresponds to just 4 joules per kg body weight, about 50 % of those affected die within 30 days ($LD_{50/30}$) as shown in Table 3.

Table 3. 50 % death rate after 30 days [19]

Species	$LD_{50/30}$ in Sv
Man	4
Rat	6
Trout	15
Bat	150
Wasp	1,000
Tabaccomosaic virus	2,000

It is evident that highly developed organisms are particularly sensitive to radiation. There is a change in human blood values with doses of 0.5 Sv already. In addition, acute symptoms such as nausea and exhaustion, hair loss, selective bleeding of the skin and sterility are the result of a dose of 1 Sv already. With a dose of 6 Sv chances for survival are minimal. The LD_{50} value for a lethal radiation dose is 4,000 mSv which would correspond to the radiation exposure of 40,000 flights from Frankfurt to Tokyo. The earlier symptoms appear and the longer they persist, the higher the radiation dose is to be assumed. Recovery takes weeks or months. Low radiation levels are more likely to lead to a higher cancer rate in the long term. The cancer risk at long-term doses of 0.1 to 0.2 Sv is epidemiologically ensured. At doses below 0.1 Sv, the assessment is unclear. The tolerable annual dose for workers in nuclear power plants is 20 mSv. Despite years of research, the health consequences and risks for astronauts during long-term stays are hardly known [20]. While radiation at ground level is about 0.3 mSv annually, it is 100 to 200 mSv on the ISS space station. For hypothetical life on a Mars station it would be about 250 mSv. In accordance with its greater distance from the Sun, Mars is likely to reach only about 43 % of the solar energy per surface area compared to Earth. However, since there is no protective ozone layer in the atmosphere of Mars, the intensity of UV radiation is considerably higher than on the surface of the Earth. In addition, sporadic solar eruptions would cause an additional risk of cancer. Table 4 shows threshold values and typical dose values.

Table 4. Threshold values and typical dose values [19]

Effect	in mSv
Maximum dose by radiation on a flight from Frankfurt to Tokyo	0.1
Average radiation in Germany	2-3
Annual threshold value for workers in Germany	20
Threshold value for damage to unborn child	100
Threshold value for life exposure of an employee	400
Blood count changes, reddened skin	500
Threshold value for vomiting	1,000
Threshold value for deaths	2,000
LD_{50} with minimum supply	4,000
LD_{50} with maximum medical care	8,000

Table 5 indicates additional annual cosmic rays.

Table 5. Additional annual cosmic rays [19]

	in mSv
0 m	0.3
2 km altitude	0.6
10 km altitude (Airbus 380)	40
18 km altitude (Concorde)	90
Space shuttle (300 km altitude)	100 to 200
Life on Mars	250

5. Drug Stability in Space

The higher radiation exposure in orbit not only creates a hazard to living creatures. Medications of the on-board pharmacy are exposed to increased radiation, especially during long-term stays. Even within 10 days, clear differences between drugs on space shuttle flights and identical sets of preparations on the ground were found. Of 15 samples, six drugs had changed significantly after 28 months on the ISS. Of the products stored simultaneously on the ground, only two had changed. The number of drugs that lost their active pharmaceutical content (API) increased in dependence on time in space. Pills became partially crumbly and clumped together. Creams dried out or liquefied. A dissociation of main components in ointments could be observed. Also, high acceleration and deceleration during transport tend not to be conducive to the stability of drugs [21]. So far, the problem has not been acute, as the ISS can quickly be supplied with new drugs whilst it is in the Earth orbit. Of course, this is not possible for long-term missions, e.g. to Mars. So far, it is hardly known which products are produced during decay and which measures need to be taken to guarantee the stability of drugs.

6. Danger from Previously Unknown Substances in Space

Outside the moderate and life-sustaining conditions on Earth, there are extreme conditions on other planets of our solar system and the universe. Large temperature differences, different gravitational forces, vacuum, but also large pressures, radiation and extreme dryness could enable the formation of unusual chemical compounds. Of course, the toxicological characteristics of these substances are still unknown. The Wet Chemistry Laboratory of the Phoenix Mars Landers found a remarkably high concentration of perchlorate salts (0.5 to 1 %) on the surface of Mars [22]. That is three to four ranges higher than on the surface of the Earth. While perchlorates are formed on Earth mainly by oxidation of atmospheric chlorine by ozone or oxygen radicals, this mechanism would be much more ineffective under Martian conditions [23]. It is therefore assumed that perchlorates are formed in several steps through high UV radiation on Mars from sodium chloride of the Mars soil. Intermediate stages are chlorites and chlorates [24]. Since perchlorates are oxidizing agents, they also make bacterial life directly on the surface unlikely. Model experiments on earth showed that perchlorates accelerated the cell death of bacteria by a factor of 10 [25]. On the one hand, perchlorates could be an easily accessible source of oxygen, but are also a source of danger for future astronauts [26]. The uptake of perchlorates leads to a reversible inhibition of iodine uptake of the thyroid gland. Iodine deficiency can lead to a deficiency of the thyroid hormone thyroxine in human beings. It might therefore be possible that the Mars struma could become a possible Mars-specific and until unknown disease on Mars.

Another problem with microgravity is the possible weakening of the human immune system, which could make astronauts more susceptible to disease. At the same time, stress factors seem to make microbes more aggressive and dangerous. Thus, in 2011 Pseudomonas aeruginosa cultures were carried on the Space shuttle missions STS-132 and STS-135. During the Apollo 13 mission, this germ had led to an urinary tract infection and finally to a kidney infection with the astronaut Fred Haise. The result was a biofilm that was larger than the one of the comparison specimen on Earth [27]. It was not the first time in space history that a specific disease was caused by a celestial body: the astronaut Harrisson Schmitt, who was the twelfth and so far last person to enter the moon, reported in December 1972 symptoms reminiscent of hay fever caused by the moon dust [28]. This was virtually the first extraterrestrial poisoning in medical history.

6. Perspectives

Former ESA astronaut Ulrich Walter dared to predict the exact date of the very first landing of human beings on Mars. If you take off from Earth on 11 April 2048, Earth and Mars would be in such a favourable constellation that the flight would only take 114 days. On Sunday, 2 August 2048, astronauts would enter successfully the surface of Mars for the first time [29]. Perhaps one day in the distant future in the 22nd century there will be a barbecue with alcoholic beverages on a permanently inhabited Mars station (at 1/3 of the Earth's gravitational force). By then, the still almost unknown field of astrotoxicology should have been explored to such an extent that it is predictable whether less or more alcohol is required to achieve the desired serenity. At present, this question cannot yet be answered.

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