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UVB can affect the immune system resulting in decreased resistance to infections and tumors.

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Abstract

As a result of depletion of the ozone layer by industrial waste compounds, all living organisms on the earth's surface may be exposed to increased amounts of UVB radiation. In man UVB radiation can cause deleterious effects on the skin and the eyes. During the last years it has become clear that UVB can affect the immune system also. Hence, UVB may affect the resistance against infectious diseases. It is demonstrated that UVB can inhibit the immune response against skin-associated infectious diseases. However, recently it became clear that UVB can also induce immunosuppression at other loci than the exposed skin. Hence, also the immunological resistance against non-skin associated infectious diseases and tumors can be affected. Recently we demonstrated that low doses of UVB can induce immunosuppression in rodents and man. This suppression was not restricted to the exposed skin. Finally we demonstrated that this immunosuppression leads to a significant suppression of the resistance against non-skin associated infections in the rat. It is noteworthy that the resistance against bacterial (Listeria monocytogenes), viral (cytomegalo virus) as well as parasitic (Trichinella spiralis) infections was inhibited and that this inhibition was correlated to a suppression of the cellular immune system. Because these data demonstrate that low doses of UVB can affect the immune system in man and rodents and because animal studies showed that this immunosuppression inhibits the resistance to infections it is worthwile to analyse the risk for increased UVB levels with respect to infectious diseases in man.

1. INTRODUCTION

A decrease of the atmospheric (stratospheric) ozone layer, induced by the emission of CFC's, may result in an increased exposure of humans to ultraviolet radiation. Especially the exposure to wavelenghts between 280 and 315 nm (=UVB) will be increased due to

ozone depletion. Aside of a beneficial effect like vitamin D production ultraviolet radiation can cause deleterious effects on human health. Most studies regarding the toxic effects of ultraviolet radiation are restricted to deleterious effects on the skin and eyes. From experimental studies it can be concluded that UVB radiation causes tumors by at least two separate mechanisms: 1) by genotoxic activity of UVB radiation and 2) by affecting the immunologically mediated resistance to tumors. Both in laboratory animals and in humans evidence has been obtained that UVB radiation can affect the immune system. Hence it is reasonable to expect that immunological resistance to infections may also be altered by UVB exposure. It is known that resistance against infectious agents that enter the body via the skin, such as Leishmania, and Herpes simplex, can be affected by UVB irradiation. Whether resistance to infectious agents that enter the body via other routes is affected was as yet not known. Because UVB radiation can induce systemic immunosuppression, suppression of immunity against non-skin associated infections (diseases), may also be suspected.

The main purpose of this research project was to determine whether UVB radiation affects the resistance to several systemic non-skin associated infectious diseases and skin tumors in man. For this purpose several infection models and a tumor model in rodents were used. Since such studies cannot be performed in human volunteers, (limited) non-invasive studies in man (blood, biopsies), rat and mouse were needed in order to compare the effects of UVB radiation on various components of the immune system (basal immune parameters). If data on susceptibility differences are obtained using non-invasive tests for basal immune parameters, effects of UVB radiation on resistance against infections in rodents may be extrapolated to man. Finally, epidemiological studies are needed to validate the extrapolated data.

2. RESULTS

In non-invasive studies dependency of immunological changes on UVB dose and species (rat, mice, man) was investigated. In all species tested macroscopic and microscopic effects of UVB exposure were studied and compared. These studies demonstrated that the skin of rodents is more sensitive to UVB exposure than that of humans and that the difference in sensitivity in primary skin effects might be due to skin thicknesses. The pathological parameters were dependent on UVB exposure (intensitity and duration dependent).

Based on these initial studies the effects of UVB exposure on several basal specific and non-specific immune parameters were investigated. The applied UVB doses were suberythemal (no reddening). Investigations with respect to changes in the number and subtype of immune competent cells in the skin as well as in lymphoid organs were performed and demonstrated that certain subtypes of lymphoid cells migrate to the skin and other subsets leave the skin. Recently, we demonstrated that lymphoid cells with UVB-induced DNA damage were detectable in lymph nodes indicating that systemic effects can occur after exposure to low UVB doses. In addition to these descriptive studies studies on immune function were carried out also. A detailed study on the UVB-induced systemic suppression of a bi-phasic contact hypersensitivity response was carried out to ascertain whether suppression of the early phase would directly lead to the suppression of the late phase (the classical delayed reaction). This appeared not to be the case. Several immune parameters such as T cell responsiveness (e.g. delayed type hypersensitivity) and natural

killer cell function were significantly suppressed by exposure to low UVB doses. This was true for humans and rodents. Differences in susceptibility with respect to these parameters were less clear than with respect to the primary skin effect studies.

The effects of UVB exposure on resistance against infectious diseases were studied in rats. Three different models for non-skin associated infectious diseases and one for a skin-associated infectious disease were used. We demonstrated that UVB exposure (suberythemal doses) can inhibit the immunological resistance against Trichinella spiralis infections in rat. Exposure to suberythemal doses of UVB after oral Trichinella infection leads to higher a number of parasites in the carcasses, indicating that the resistance was impaired. Recently, we demonstrated that the specific lymphocyte response to Trichinella was significantly inhibited. This points to an effect of UVB radiation on the cellular (T cell mediated) immune system. Because Trichinella spiralis infections still occur, e.g. in Eastern Europe, effects of UVB on this animal model may be relevant. Additionally, we demonstrated that suberythemal doses of UVB inhibited the resistance against a intraveneously Listeria monocytogenes infection. Especially the specific T cell response to this pathogen was inhibited by UVB exposure. Listeria infections are still a problem for human health especially for humans with a depressed immune system such as transplantation patients, babies and eldery persons. As was found for the parasitic and bacterial infection model also resistance to systemic cytomegalovirus infections was inhibited by UVB exposure of rats. Cytomegalovirus infections are still a health problem in immunosuppressed humans such as transplantation patients. For this reason this infection model in rats is very relevant for the human situation. In sum, resistance against several non-skin-associated infectious diseases that also occur in humans, especially in humans with a suppressed immune system such as in transplantation patients, can be inhibited by UVB exposure. Finally, we demonstrated that UVB radiation also affects the resistance against Herpes simplex skin infections. In man this disease is suggested to be evoked by UVB: e.g. cold sores in skiers and sun bathers. This latter infection model appears particularly suited to compare effects of UVB on resistance in humans and rodents.

In addition to these infection studies we demonstrated in an extensive time lapse study in hairless mice that prior to macroscopically observable UVB-induced skin tumors, alterations in composition of lymph node cells and skin immunocompetent cells ocurred. Mice with these immune alterations became incapable of rejecting UVB-induced skin tumors whereas normal (non-exposed) mice rejected these transplants almost immediately. The early immunological changes observed did not coincide with, but amply preceded the time by which the mice started to accept the tumor implants. These findings confirmed and timed the UVB-induced immune alterations in the course of the induction of skin cancer in the hairless mouse model.

Using all the obtained data with respect to UVB-induced alterations in several immune parameters (systemic and local) in rodents and man, and UVB-induced alterations in resistance against infectious diseases in rodents, a basis for risk estimation of exposure to elevated UVB levels is formulated. Risk estimation until now was only restricted to skin cancer, and did not explicitely taken into account effects on the immune system. Now, there are several lines of evidence that immune alterations play an important role in the induction of skin cancer and probably also in severity and incidence of infectious diseases.

3. CONCLUSION

From all the experiments that were done we conclude that low UVB doses, i.e. sub-erythemal doses, can affect the immune system. It is remarkable that this immunosuppression is not restricted to the exposed site (skin). Even in the spleen and lymph nodes immune alterations have been found using several different tests. The effects found were not species specific although the primary skin effects in humans tended to be less severe than in rodents. From animal experiments we conclude that the UVB induced alterations of the immune system play a significant role in the decreased resistance against tumors and infections in rats and mice. With respect to the infection studies it is demonstrated that UVB radiation can affect the resistance against skin-associated infectious diseases, such as the well known cold sores (i.e. Herpes simplex infections) as well as the resistance against non-skin-associated infectious diseases (e.g. oral parasitic, intraveneous bacterial and viral infections). The data obtained, viz. regarding immune effects in man and rodents, and regarding the resistance against infectious diseases and tumors in rodents, form a basis for a better assessment of effects on the incidence and severity of infectious diseases and tumors in UVB-exposed populations. In future these data will be used for calculation of risk from an ozone depletion. Until now, resistance against infectious agents and tumors can only be studied in rodents, and therefor the effects in humans have to be extrapolated from the animal studies. Nevertheless, there are possibilities now to study effects of UVB radiation on the resistance against certain infectious diseases in humans. Some of these infectious diseases are even thought to be related to the induction of skin cancer (human papilloma virus infections). Finally, suitable epidemiological data are needed to improve the human studies and validate the extrapolation of animal studies to man.

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