Edelmetalle/Übergangsmetalle und Umwelt: Kfz-Katalysator verantwortlich für Erbschäden und Ozonloch?

Reinhold Kiehl

RKI-Institute, Laboratory and research for molecular biology/medicine, Saliterweg 1, D-93437 Furth im Wald, Germany, Email: kiehl@rki-i.com, Internet: www.rki-i.com.

Abstrakt

Hauterkrankungen, Atemwegserkrankungen und vor allem Asthma, Erbschäden sowie Krebserkrankungen, wie Leukämie, steigen rapide seit der Einführung des Katalysators in den westlichen Ballungsgebieten - ab 1990 auch überproportional in den Ostblock-Staaten mit Wegfall der Mauer und Austausch alter Kraftfahrzeuge gegen Katalysator-Autos (1-6).

Verantwortlich dafür sind die in unsere Atmosphäre geblasenen feinstverteilten Metalle, wie Quecksilber, Cadmium, das am häufigsten verbreitete Kontaktallergen Nickel sowie - der meist signifikante atmosphärische "asthmatische" KFZ-Umwelt-Ausstoß Platin, Palladium, Rhodium, mit oder ohne die ebenfalls zur Emission gelangenden aliphatischen und aromatischen Kohlenwasserstoffe sowie Rußpartikel (9-11).

Gewarnt wurde vor 15 bis 20 Jahren schon von Experten mit Ergebnissen aus entsprechenden Versuchen mit dem Katalysator in den USA (12), ohne daß irgend jemand darauf gehört hätte. So schneit es in Grönland seit Einführung des Katalysators bis zu 120 mal höhere Konzentrationen an Platin und Rhodium (13). Die westliche Hemisphäre wird mit den Platingruppen-Metallen in größtem Ausmaß kontaminiert, neben der schon bestehenden Kontamination durch Quecksilber aus fossilen Brennstoffen.

Ein PKW mit Katalysator verliert im Schnitt 1.5 Mikrogramm feinst verteiltes Platin/km Fahrt. In einem Stau mit langsamer Fahrt sind dies etwa 1.1 Gramm. In einer Großstadt wie München werden pro Tag ein Gramm Platin freigesetzt oder ca. ein halbes Kilo/Jahr plus Kohlenwasserstoffe und Rußpartikel (14-16).

Die direkte Einatmung durch Fußgänger sowie Schwangere und Kleinkinder erklärt die Erkrankungsraten. Diese Tatsache ändert sich auch nicht mittels Verharmlosung durch die Kraftfahrzeug-Industrie oder andere (17). Gegen die entstehenden genetischen Defekte gehen unsere Gentechniker nun vor, ein stark wachsendes neues Spielfeld mit neuem Markt: Wir ändern die Evolution im Schnelldurchgang...

Die Hydroxid-Radikal-Konzentration in der südlichen wie nördlichen Hemisphäre variieren signifikant seit zwei Dekaden. Das Hydroxyl-Radikal ist die dominante oxidierende Chemikalie in der Atmosphäre und damit direkt involviert in den Ozon-Haushalt und den "Treibhaus-Effekt" (18).

Radikal-Reaktionen in dieser "Metall-Sauerstoff-Stickstoff-Kohlenstoff-Wassersuppe" sind verantwortlich für das Ozon-Loch und den Treibhaus-Effekt. Die Katalysator-Metalle und damit der KFZ-Verkehr sind für steigende Erkrankungsraten, Ozonloch, Treibhaus-Effekt, Klima-Änderung und Waldsterben "der" Verursacher und nicht Kohlendioxid mit seinem Anstieg (19,20,21).

Die Konsequenz dürfte damit klar sein: schnellste Reduktion der Metalle aus unserer Atmosphäre (neben der Reduktion von CO_2) – vielleicht haben wir Glück und die Atmosphäre erholt sich – so wie sie es schon einmal einige Millionen Jahre vorher zur Zeit des Aussterbens der Dinosaurier getan hat.

Abstract

Skin diseases, diseases of the respiratory tract and above all asthma, genetic defects as well as cancer, including leukemia, are rapidly increasing in the western conurbations with the use of catalytic converter

(cat)cars – since 1990 very heavely in the east-Bloc states:fall of the wall and exchange of old cars without cat against cat cars [1-6].

Responsible for this fact are in the air finest distributed metals, like mercury/mercurials, cadmium, the most commen occupational as well as public contact allergen nickel [7] and the most significant atmospheric asthmatic pollution platinum [8], palladium, rhodium (automobile exhaust) with or without heavy pollutions of aliphatic and aromatic hydrocarbons , as well as root particles [9-11].

There came already warnings about 15 to 20 years ago by american experts, who carried out appropriate experiments using these catalytic converters [12]: Nobody, as usual, heard to them. Now, since the use of catalytic converters, it is snowing in Greenland over 120 times higher concentrations of platinum and rhodium [13].

The western hemisphere is assumed to be contaminated in alarming proportions in the near future with the platinum group metals, beside the already existing contamination with mercury out of fossil fuel.

A cat car loses on average 1.5 microgram finest distributed (colloidal) platinum (plus palladium and rhodium) per kilometer drive. In a tailback and a slow move are these 1.1 gram. In a metropolis like Munich about 300 to 400 gram per year including hydrocarbons and root particles [14-16].

The direct inhalation by pedestrians/infants and pregnant woman explains the increasing disease rates. That fact can not be changed with minimization by the automobile industry or by others [17]. The mechanisms acting are the affinity of nickel for nitrogen and not for sulfur. Colloidal platinum/palladium and nickel for instance have a preference for carbon, alkene, alkine; alkylate, catalyse additive reactions, oxidations, hydrogenations. Platinum (Cis-Platinum) inhibits/stimulates proliferations/IgE-synthesis. Against the emerging genetic defects are our genetic engineers now fighting, a heavely expanding new field with new market; We are changing the evolution in high speed.

There is evidence for substantial variations of the hydroxyl radical (OH) concentrations in the Southern and Northern Hemisphere during the last two decades. The hydroxyl radical is the dominant oxidizing chemical in the atmosphere and is therefore directly involved in the ozone depletion and the greenhouse effect [18].

Radical reactions in that "metal-oxygen-nitrogen-carbon-water soup" are responsible for the ozone gap and the greenhouse effect. The catalyst metals, and therefore the automobile traffic, are for rising disease rates, ozone gap, greenhouse effect, climate change and forest dieback "the" responsible causes and not carbon dioxid with its dramatic rise [19,20,21].

The consequence should therefore be clear: fastest reduction of the metals out of our atmosphere (beside reduction of carbon dioxid) – maybe we are in luck and the atmosphere is regenerating – like it did some millions of years ago at the time of the saurien dead.

Referenzen:

1. Schramm, J. Instrumentelle und Umweltschutzanalytik, FH Niederrhein, Krefeld (1994)
2. Wichmann, H.E. Clin. and Exp.Allergy 26, 621-623 (1996)
3. Cullinan, P., Newman Taylor,A.J. Clin. and Exp.Allergy 27, 41-46 (1997)
4. Kiehl, R. IFCC Proc., 17 Int.Symp., Nice, 467-482 (1998)
5. Kiehl, R. IPRAC Allergie (CS) Abstrakta, Roenik (Suppl.I),72 (2001)
6. Arbeitsgemeinschaft Bevölkerungsbezogener Krebsregister in Deutschland/ Robert Koch Institut, Saarbrücken 2002, ISBN 3-88718-153-0; www.rki.de/KREBS
7. Büdinger, L., M.Hertl, Allergy 55, 108-113 (2000)
8. Kiehl, R. J.Lab.Med. 24, 465-466 (2000)
9. Alastair, C.L. et al. Nature 405,7-9 (2000)
10. Science 277, News and Comment, 25 July (1997)
11. Kiehl, R. Biotechnology in Bavaria I, 45-46 (2001)
12. Günther, A. Ulmer Verlag, D-7201 Tunningen (1991)
13. Communication of the RSC, Great Britain (2001)/Environ.Sci.Technol.2001,35,p.835
14. Kiehl, R. Neurodermitis, Umwelt und Allergie 38, 37-38 (2001)
15. Schierl, R., Fruhmann, G. Sci.Total Environ. 182, 21-23 (1996)
16. Schierl, R. Microchemical Journal 67, 245-248 (2000)
17. Hoppstock, K. Nachrichten aus der Chemie 49, 1305-1309 (2001)
18. Prin, R.G. et al. Science 0,Issue of May (2001)
19. Kiehl, R. Deutsches Patent und Markenamt, PCT/02/01966, 28.Mai (2002)
20. Kiehl, R. GDCh/ADUC Chemiedozententagung 2004, 7.-10.März, Universität Dortmund
21. Kiehl, R. Internet, www.rki-j.com, www.dr-kiehl.net, pdf-files and references.

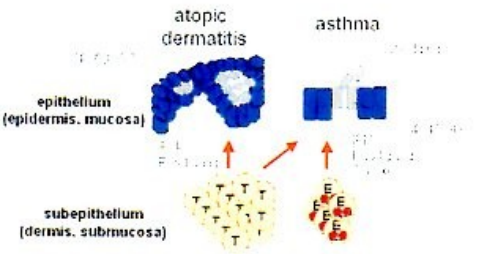
Precious metals/transition metals and environment: Catalytic converter responsible for genetic defects and ozone hole? Continuation of the lecture given by R.Kiehl at IPRAC, April 1 to 4, 2001, Praque, Czech Republic, Allergie, Abstrakta, Rocnik 3, Suppl1, 2001:

Atopy/Contact Dermatitis/Asthma:Metal Ions/Cd;Hg;Ni;Pt;Pd

Key words: g-interferon, cytokines, electron transfer chain, redox potentials, metals, diseases, ozon gap.

Abbreviations:IL=interleukin,IFN=interferon,APMSF=(4-amidinophenyl)-methanesulfonyl-fluoride,NEM=N-ethylmaleimide,pCMB=p-chloromercuribenzoate,
Diamide= azodicarboxylic acid bis (dimethylamide), DMPS = dimercaptopropan-sulfonate.

Mercury, metalloproteases, IgE-level, inflammation and allergic manifestations



In search for an assay system more closely related to the in vivo conditions of atopic eczema patients, we decided to directly investigate the blood samples of these patients. During our first attempt we titrated the blood samples with activators and inhibitors of proteases, since some of these compounds were thought to be involved in triggering atopic eczema. Particularly the metalloprotease activator mercury should have been able, in our opinion, to influence gIFN-levels by activation of metalloproteases for degradation of this important regulatory factor. Mercury has been suspected for decades now of triggering allergic manifestations via the immune system.

The effect of mercury on IgE-levels was seen at concentration ranges of 0,5 to 1 mM; concentrations which are about 1 mio times higher than the normal range in blood of control or atopic eczema persons. Mobilization of mercury by DMPS results in 10^2 to 10^3 times higher values in these persons, which is still about 10^2 to 10^3 times lower than our measured effective concentrations of Hg on IgE-levels. Nevertheless, someone describes immune changes (in the lymphocyte-subpopulations) induced in their opinion by mercury mobilization. However, these changes, especially in patients with allergic diseases, were not verified. In another study high dosages of mercuric-chloride *(50 µg*/100 g body weight) were repeatedly injected into rats, which corresponds to about *5* mg/l blood (a concentration near our described effective concentrations), with enhancement of antibody production. Thus, low toxic mercury concentrations seem not to be responsible for the changes in IgE-levels in our patients.

Matrix metalloproteinases (collagenase, gelatinase, stromelysin) are highly glycosylated enzymes, active at neutral pH, which require intrinsic Zn^{2+} and extrinsic Ca^{2+} for full activity, and are therefore inhibited by chelating agents (like EDTA) and have the ability to degrade, for example, the extracellular matrix. They are secreted from the connective tissue cells such as fibroblasts and from neutrophils as inactive proenzymes, and can be activated by treatment either with proteinases such as serine-proteinases, or with different mercurial compounds, or reactive oxygen species (ROS). They are also inhibited by their specific inhibitor TIMP or α^2 -macroglobulin. The signal for upregulation of their secretion is suppressed by immunosuppressive drugs, like glucocorticoids .

Activation of isolated metalloproteases requires μM concentrations of mercurials: 10 μm $HgCl_2$, for instance, activates about 40% of the proteases (collagenase) within approximately 4 hrs. These conditions were obtained in our patients after mercury mobilization and may therefore be responsible for glucocorticoid-sensitive inflammations . However, under normal conditions the circulating protease and lactoferrin concentrations in the patients were found to be normal. The collagenase and gelatinase assays have been done by ELISA. ELISA measures only protein concentrations. In blood samples of healthy donors, metalloproteases are inhibited by TIMP, protected by α^2-macroglobulin and the anticoagulant heparin from reaction with substrate or binding to antibodies (for instance during ELISA), which leads to the lowest concentrations (and activities). In EDTA plasma, α^2- macroglobulin is inactive and residual heparin and/or TIMP protect and/or inactivate(s) only part of the present latent proteases resulting in moderate concentrations (collagenase ca. 90ng/ml gelatinase ca. 600 ng/ml, and lactoferrin ca. 300 ng/ml at healthy donors, Tschesche, personal communication) and activities. In the sera (coagulated blood), α^2- macroglobulin is inactive, heparin missing and therefore almost all the metalloproteases are activated by oxidation (below). As to expect, the highest concentrations (and activities) of the proteases (and of lactoferrin) were then obtained in the sera.

The few measurements with capillary blood samples (collected under heparin protection) of affected skin areas (areas under acute inflammation) demonstrate that at these areas activation processes exist. The few heparin molecules, possibly in here available, may not be able to block the high concentrations of free latent and/or activated metalloproteases for binding to antibodies during ELISA (competition). On this ground, a heparin therapy should not work.

We could show (1) that circulating immune complexes and IgE in the patients blood activates the coagulation system with elevation of platelet aggregation and histamine release with further enhancement of aggregation (thrombosis). This process could be related to significantly lowered diamine-oxidase activities of platelets. We now conclude that this process starts with rising IgE concentrations in the circulating blood or affected skin areas (activation of the contact system by surfactants, etc; contact allergy). Platelets aggregation results presumably in a changed energy metabolism in these particles with build-up of vitamin K2 and H_2O_2/ROS, inhibition of diamine-oxidase by ROS (H_2O_2) with elevation of histamine, inactivation of α_2-macroglobulin and activation of metalloproteases by ROS/ H_2O_2(2). ROS may also be produced by prolonged exposure of skin cells to UV-light and responsible for development of skin carcinomas.. Nitric acid (NO) seems not to be a physiologic regulator of the cardiovascular system. However, abnormalities of the L-arginine: NO pathway could contribute to the pathophysiology of diseases like thrombosis .

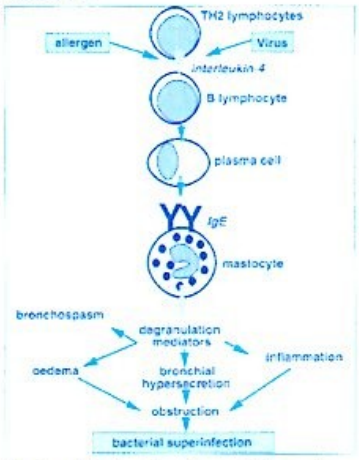
gIFN-molecules were significantly degraded by metalloproteases (at least by activated leucocyte collagenase) under in vivo conditions, although our in vitro assay showed no such behavior. However, one should keep in mind that the concentrations of the circulating gIFN molecules are very small and in the concentration ranges of most hormones. Degradation of two plasma components, namely Cl-inhibitor and α_1 -proteinase inhibitor, by metalloproteases has already been demonstrated. The implication for metalloprotease regulation is evident, and the impact of the changing active gIFN-concentrations on the IgE-levels of atopic eczema patients will be discussed below. On this point, we compared total IgE measurements using samples of circulating blood with skin Prick-tests and skin Epicutanous-tests. As expected, the measurements do not match either (2). The standardized titration of blood samples from different patients (IgE ca. 1000 U/ml) with 1 mM $HgCl_2$ resulted in unexpected positive and negative variations (> 50 %) of their IgE-values, suggesting involvement of a redox reaction in the Hg-IgE-interaction: Hg^{2+} is, like Cd^{2+}, able to react as a dithiol reagent (3a,b). The metalloprotease inhibitor EDTA elevates IgE-levels (at least in the experiments where Hg^{2+} induces positive variations). The EDTA results may be interpreted in

favor of a direct influence of the metalloprotease on IgE concentrations, however the results of the Hg^{2+} - titrations are in direct contradiction to such an interpretation.

The serine protease inhibitor APMSF itself has no effect on IgE-level, which means that this protease is not involved in IgE-regulation either directly or indirectly, and serine proteases are not involved in our measured metalloprotease activities.
APMSF probably interacts with serine residues after they are liberated by EDTA treatment, and thus prevents upregulation of the IgE-level due to EDTA. This suggests the involvement of external Mg^{2+} - or Ca^{2+}- sensitive serine residues in the signal tranduction pathway leading to elevation of IgE levels.
The detergent Triton X- 100 (and probably other detergents too) drastically lowers IgE-levels, probably by liberating IgE-degrading proteases from their storage compartments . The IgE-level was also reduced by cycloheximide, a protein synthesis inhibitor, which shows that ongoing IgE production is blocked and indicates that de novo IgE synthesis is measured. A similar result, although during days of growing, has been obtained in cell culture systems .

Patients' IgE-level in the circulating blood system is regulated by degradation and (re)synthesis (secretion seems not to be a rate-limiting step), and these two processes are regulated by various factors, including interleukins and gIFN. We were able to demonstrate this well-known fact, during relative short time intervals (=minutes in harmony with the O_2^- -build- up in neutrophils) in our simple assay system, although the background level of IgE was very high (70 to 90 %). It was then possible to calculate degradation, as well as synthesis rates of the patients' steady state IgE-level, by doing a few assays.
Furthermore, and even more importantly, the results obtained with Hg^{2+} indicate the involvement of a redox reaction in the regulation of IgE synthesis (2).

Involvement of a redox/thiol-disulfide interchange mechanism in the regulation of IgE-synthesis



This dithiol/disulfide redox state is sensitive to Hg^{2+}, Diamide, gIFN and IL- 4, hut not to 1 mM Zn^{2+} (2). gIFN probably directly or indirectly changes the conformation of the involved protein, etf (2) in such a way that two associated thiols become vicinal and able to react with Hg^{2+}. Hg^{2+} itself keeps this conformation and thus lowers the effective concentration of gIFN by a factor of 10^2 to 10^3 or more . IL-4 reacts antagonistically to gIFN in blood samples and in cell cultures, although in opposite directions and at different time scales (minutes vs days) . The interaction of conformation with redox state at the existing gIFN-concentrations in our patients explains the highly varying IgE values in the blood samples of these patients on addition of Hg^{2+}. The described mechanism relates to the origin of BSE, Creutzfeld-Jakob and similar diseases (2).

Our ineffective titrations of the redox state, indicated by the various IgE levels, with extremely high concentrations of glutathione (ox. or red.) (2) for plasma, demonstrate clearly that the thiol groups involved were located inside the involved B cells: glutathione cannot cross cell membranes. Another point is that externally delivered glutathione is then, of course, not able to replace Hg^{2+} or

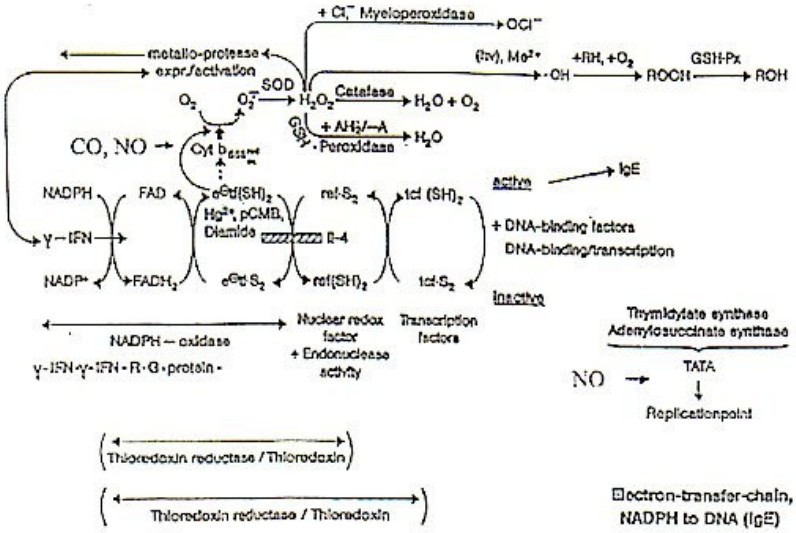
Diamide in the described dithiol/disulfide interchange mechanism. Hg^{2+} and Diamide, effective at high concentrations, react inside the cells , most likely with a dithiol-containing protein localized, at least for some time, on the inner cell membrane. Cytosolic glutathione should not be involved: the results and the described mechanism require the involvement of a membrane-bound protein. NEM is ineffective although reacting normally with reduced cellular glutathione and the cellular glutathione concentrations were too high (up to 10 mM) to be involved in the Hg or diamide-induced elimination of IgE-synthesis. It is concluded, that etf is a FeS-protein. The different results obtained when using blood samples or cell cultures may be explained by the conditions in which the cells live. We used „in vivo„ conditions for our experiments, in contrast to cell cultures which were grown in artificial systems using mitogen-stimulated B cell proliferation.

Elektron transfer chain, NADPH to DNA

The redox signal of gIFN for O_2^- or IgE production (activation process) is probably mediated by its receptor to the NADPH oxidase, most likely at first to the NADPH-binding subunit via G-protein (Rac-2). This system, thus, very much resembles the receptor-linked membrane-bound adenylate cyclase and is starting point of the e-transfer chain, NADPH to DNA (IgE) (2). The defect in NADPH to DNA (IgE) at atopic eczema patients lies at the level of etf/ref . The question about the

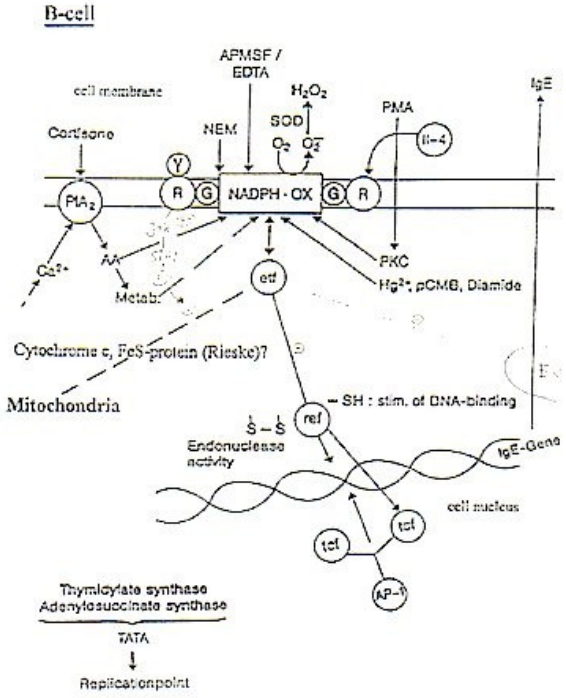
Disturbance of the dithiol/disulfide-balance, shift of the redox potential by (incl.):
Cd^{2+}, Hg^{2+}, Diamide, Aldehyde, Anhydride, Isocyanate, Isothiocyanate, HSO_3^-/SO_2, N_3^-, O_2^-, NO, O_3.

CO, NO (CO_2, NO_2): Reaction also with the NADPH-Oxidase (DNA).



IL-4 interference in the described redox regulation of IgE synthesis is difficult to answer. The mechanism of signal transduction by the IL-4 receptor is rather obscure. The described down regulation of gIFNmRNA and gIFN production in mitogen activated T-culture cells by IL-4 takes days and is therefore related to the late responses of gIFN on endonuclease and its antiproliferative

effects (2). During short time intervals, IL-4 transduces opposite to gIFN redox signals. Coupling of the IL- 4 receptors to the electron transfer chain at the level of etf/ref (via G protein?) may be responsible for this behavior . The down regulation of IgE level, the production of several cytokines (IL-1, TNF incl.), as well as gIFN), prostaglandin E2 and superoxide production by IL-4 implies the possibility that IL-4 may play a role as an antiinflammatory cytokine .



REGULATION OF IGE-SYNTHESIS

Extremely high serum IgE levels exist in patients with the so called hyper IgE syndrome. in this case, regulation by IL-4 or gIFN is almost impossible and the electron transfer chain should be in the full reduced form. The defect in NADPH to IgE for electron-transfer is most probably located at the level of etf/ref as described for the normal atopic eczema patients. All the factors regulating NADPH oxidase also, of course, influence the IgE level. An important role in modulating IgE concentrations then is also played by phosphorylation and dephosphorylation of the involved proteins by kinases (e.g. PkC) and phosphatases. An indirect influence on the IgE level exists (as desribed) under oxidative stress conditions .

The redox potential is responsible for stress protein IgE or 0_2-synthesis and proliferation

The adaption of cells to oxidative stress , to heat shock, to environmental stress, etc. is nothing more than their natural defense mechanism for protection against injury .

The general scheme of activation of this defense mechanism seems to be the use of stimulatory or inhibitory cytokines/ hormones including, for instance, tumor necrosis factor (TNF) and IL-1 control NADPH oxidase (nonphagocytes), TNF and IL-1 control collagenase, and gIFN and IL-4 control IgE. In most (or all?) cases, the activation of NADPH oxidase (O_2 production) occurs simultaneously to the expression of former enzymes.

In the case of IgE synthesis (and probably also in the expression of some other compounds), environmental pollutants assumed to induce atopic eczema were able to react irreversibly with the involved essential dithiol / disulfide redox state. The pollutants include formic aldehyde, sulfide

/SO_2, isocyanates, anhydrides, etc. These compounds keep the electron transfer chain in the reduced form (low or no O_2 production) and, under activating (defence) conditions, the IgE concentrations rise to pathological ranges. The oxidized form is not able to synthesize IgE but instead O_2, and the risk of mitogen stimulated proliferations (leukemia, carcinomas and CGD) ist extemely high. Another compound, CO (and NO), binds to the NADPH oxidase , preventing the reduction of O_2 and thereby shifting the electron transfer chain to the reduced state, which is accompanied by the enhanced probability of IgE synthesis. Depending on concentration, most compounds have proven to prime cell proliferation in an animal model and in human studies .

Mitochondrial oxidative phosphorylation serves as sole producer of energy

B-cells have a considerable need for energy. Their proliferation, synthesis and excretion of immunoglobulins require this energy in the form of nucleotide-triphosphates and their fuel is glutamine instead of glucose . Thus, it is not surprising that the process of NADPH oxidase activation (IgE synthesis) and regulation is coupled to ongoing mitochondrial energy formation . All the compounds influencing mitochondrial energy formation (2) then also influence IgE and O_2-level and connects to psoriasis vulgaris (4) and AIDS (2). Dermal and intestinal dysbiosis, food, as well as psychogenic stress (2) are the main triggering factors of allergic manifestations. Polysaccharidic, as well as protein antigens of C. albicans, play a definite role in inducing allergic reactions in patients . Carbohydrate for instance, delivered by food, is a growth factor for these fungi and weakens immune response by changing the energy metabolism of lymphocytes .
Psychogenic stress elevates norepinephrine levels, lowers dependent cellular cAMP concentrations (2,5) and weakens thereby immune response (arachidonic acid, prostaglandin, leukotriene, cytokine concentration, etc.) and elevates IgE concentration. The greatest number of specific IgE antibodies are developed against food- or inhalative allergens. It should be stressed that the total (unspecific plus specific) IgE concentrations were normally 10^2 to 10^3 times higher than the measured specific ones. Perhaps the gIFN independent IgE production by cultured cells on IL-4 and CD 40 stimulation is related to this fact. The first expression of specific IgE antibodies may be purely incidental and resembles autoimmune diseases. The described pathogenesis of atopic eczema and leukemia (proliferation) relates to the development of AIDS (2).

Ni, Pt; Pd: Contact dermatitis/ Asthma

Tumorpromotion in verschiedenen Organen

Haut

Experimentelle Modelle

Mäuse sind für Tumorinduktion in der Haut besonders empfindlich. Als Initiatoren kommen meistens polycyclische aromatische Kohlenwasserstoffe wie das Dimethylbenzanthrazen oder das Methylcholanthren, aber auch andere Kanzerogene (Tab. 5) zur Anwendung. Sie werden meist auf die Haut gepinselt, können aber auch systemisch appliziert werden. So erzeugt bereits eine einzige Injektion von Cisplatin oder Urethan initiierte Zellen in der Haut, aus denen durch anschließende Promotionsbehandlung Papillome entstehen können. In vielen Hauttumoren (Karzinomen und Papillomen) sind Ha-ras-Gene nachgewiesen worden, die durch Punktmutation aktiviert sind. Je nach verwendetem Kanzerogen sind die Kodons 61 oder 12 betroffen (Tab. 5). Die Art der Mutation ist charakteristisch für den verwendeten Initiator. Normale Haut in der Umgebung der Papillome zeigt diese Mutation nicht. Offenbar lösen Initiatoren in einigen Basalzellen während der Initiation diese Punktmutationen aus, die den Zellen im Rahmen der Promotion einen Wachstums- oder Selektionsvorteil verschaffen.

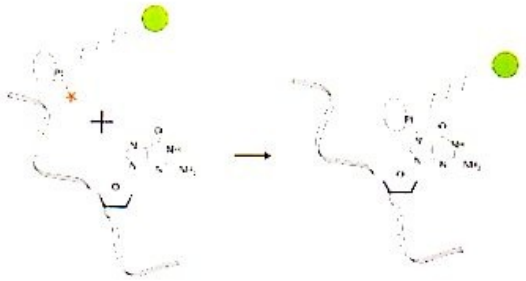
Die Promotionsphase wird nach einer Ruheperiode von etwa einer Woche begonnen, in der sich die Haut von den unmittelbaren Wirkungen des Kanzerogens erholen kann. Die Promotoren werden wiederum lokal auf die Haut aufgebracht.
Einer der effizientesten Promotoren ist das 12-O-Tetradecanoylphorbol-13-acetat (TPA). Als erste Wirkung läßt sich eine deutliche Reizung und Hyperplasie der Haut feststellen, nach 5 bis 7 Wochen erscheinen die ersten gutartigen Papillome.

Tab. 5: Initiatoren in der Mäusehaut.

Initiator	ras-Mutation	
	betroffenes Kodon	Mutation
Dimethylbenzanthrazen	61	A→T
Methylcholanthren	61/13	A→T/G→T
Methylnitrosoguanidin	12	G→A
Ethylnitrosoharnstoff	12	G→A
Urethan	61	A→T
Cisplatin	61	A→T
UV-Licht	61	C→A/A→T

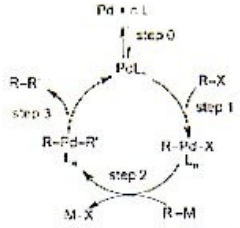
Skin diseases, diseases of the respiratory tract and above all **asthma**, genetic defects as well as cancer are rapidly increasing in the western conurbations with use of cat cars - since 1990 very heavely in the east-Bloc states/ fall of the wall and exchange of old cars without cat against cat cars (6,7).

The most commen occupational as well as public contact allergen Ni (8) and the most significant **atmospheric asthmatic pollution Pt(Pd)** (9) (automobile exhaust) are responsible for this fact (6,7,9): In the air finest distributed Pt at a metropolis like Munich results in about 300 to 400 g/ year plus haevy pollutions of aliphatic and aromatic hydrocarbons (10), root particles (10-12) and a direct inhallation by pedestrians/ infants and pregnant woman. The **mechanisms** acting: Ni does not bind to sulfur but to N. Colloidal Pt(Pd) and Ni for instance have a preference for C, alkene, alkine; alkylate, catalyse additive reactions, oxidations, hydrogenations. Pt (Cis-Pt) inhibits/ stimulates proliferations/ IgE-synthesis.



Direct labeling without enzymes
Using Nucleic Acid Labeling Kits:
A derivative of cis-platin reacts with the N-7 position of guanine residues, providing a stable linkage between the nucleic acid and the fluorescent label (ULS = Universal Linkage System, Ulysis™ Nucleic Acid Labeling Kits).

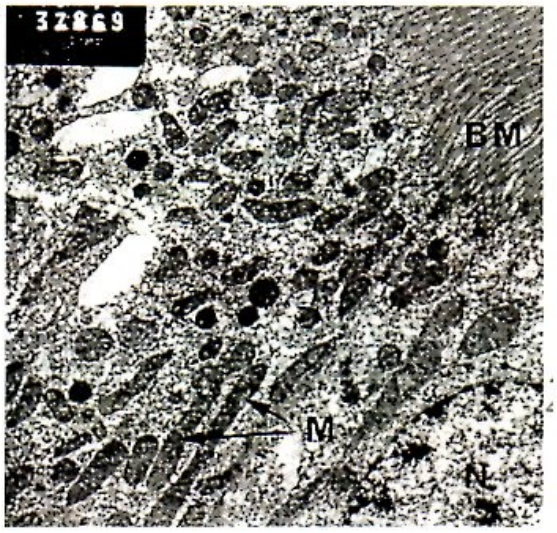
cross-coupling reactions



X: I, Br, Cl, OTf, OSO_2R, SOR, SR, N_2^+, $OP(OR)_2$
M: $-BR_2$, $-SnR_3$, $-ZnR$, $-SiR_2OH$, $-AR_2$
$-ZrR_3$, $-Cu$, $-MgR$, $-Li$, $-MnX$, $-HgR$, $-GeR$

Scheme 1.
General mechanism of the palladium catalyzed cross-coupling reactions

a



b

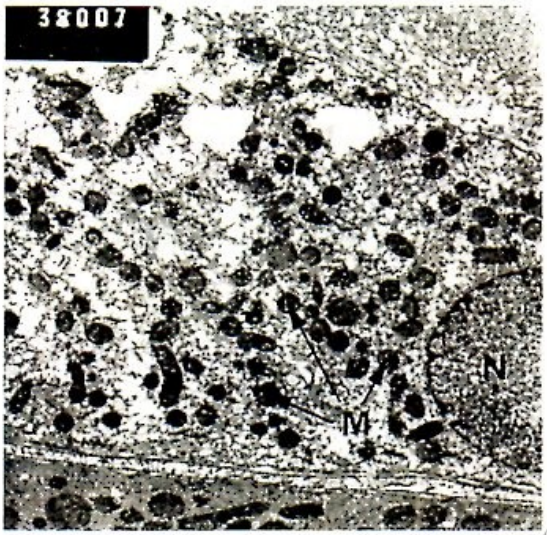


Abb. 11: Transmissionselektronenmikroskopische Aufnahme vom S3-Segment des proximalen Tubulus nach Behandlung von Ratten mit Cisplatin.
a) Kontrolle; b) 3 Tage nach der Behandlung von Ratten (5 mg/kg, i. p.) treten starke Veränderungen der Mitochondrien (kugelförmige) ein. BM = Bürstensaum; M = Mitochondrien; N = Zellkern (X 16300).

A summation of the causes for multifactorial diseases, e.g. allergies, respiratory tract diseases and asthma is described by us (13).

1.Kiehl R and Ionescu G. Mediators of Inflammations 1993,2:403-406.
2.Kiehl R IFCC-Proc. of the 17th Int. Symposium on "The Confluence of Critical Care Analysis and Near Patient Testing", Nice, 1998 June 4-7, p.467-482; Habilitation, University Munich, Med.Fakulty 1995; Boehringer Ingelheim/ Bender Wien 1993.
3a,b.Stiggall DL et al. BBRC 1979, 196, 638-644; Kiehl R. FEBS Letters 1980,109:280-282.
4.Kiehl R and Ionescu G. Acta Dermato Venereologica1992,72:253-255.
5.Kiehl R. Psoriasis Magazin (Deutscher Psoriasis Bund e.V.)1992,4:8-9.
6.Kiehl R. Neurodermitis, Umwelt-Haut und Allergie 2001,38:37-38.
7.Kiehl R. IPRAC Allergie (CS) Abstrakta, Rocnik 2001,3(Suppl.1):72.
8.Büdinger L and Hertl M. Allergy 2000,55(2):108.
9.Kiehl R. J Lab Med 2000,24(10):465-466.
10.Alastair CL et al. Nature 2000,405:778-781.
11.Cullinan P and Newman Taylor AJ. Clin. and Exp. Allergy 1997(27,1):41-46.
12.Science 277,25th of July 1997, News and Comment.
13.Kiehl R Biotechnology in Bavaria (Profiles, Portraits, Perspectives – Global Partners) 2001,1:45-46.
14.Chem.in Britain, April 2001, p.15/ Environ.Sci.Technol.2001.35,p.835.
15. Hoppstock K. Nachr.Chemie 2001, 49, 1305-1309.
16.Prim RG et al. Science 2001, 0, Issue of May.
17.Kiehl R. Bioforum 2002, 10, 618.
18.Kiehl R. Straubinger/Landshuter Zeitung, 17.Sept 2002.
19.Kiehl R. Int.Patent PCT/DE 02/01966.
20.Kiehl R. Internet at www.rki-i.com, (html-, pdf-) files.

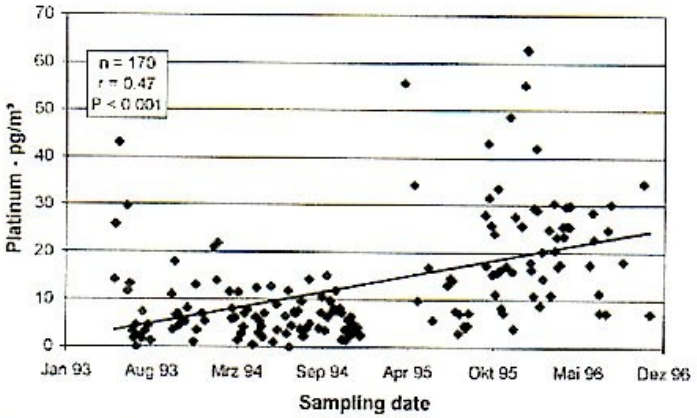
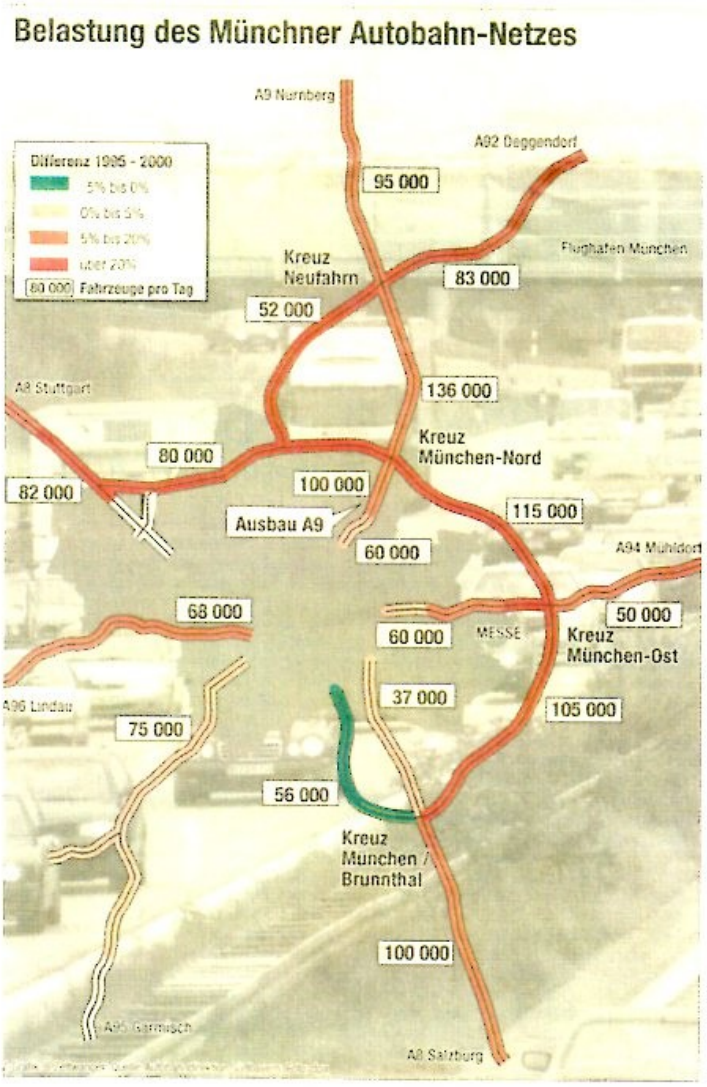


Fig. 1. Airborne platinum concentrations in Munich city buses and tramways during regular rides.



Bücher: F.A.Cotton/G.Wilkinson, Anorganische Chemie, VCH
R.Kiehl, Buch, Literatur und Dateien unter www.rki-i.com
H.Marquardt, S.G.Schäfer, Lehrbuch der Toxikologie

Katalysator verantwortlich für Ozonloch

Reinhold Kiehl
RKI-Institute, Laboratory and research for molecular medicine/biology, Saliterweg 1, D-93437 Furth,
Email: kiehl@rki-i.com , Internet: www.rki-i.com

Haut-, Atemwegserkrankungen und vor allem Asthma, Erbschäden sowie Krebserkrankungen, wie Leukämie,steigen rapide seit der Einführung des Katalysators in den westlichen Ballungsgebieten. Seit 1990 auch überproportional in den Ostblock-Staaten mit Wegfall der Mauer und Austausch alter Kraftfahrzeuge gegen Katalysator-Autos[1-3]. - - Verantwortlich dafür sind die in unsere Atmosphäre geblasenen feinstverteilten Edelmetalle, wie Hg, Cd, das am häufigsten verbreitete Kontaktallergen Ni[4] sowie - der meist signifikante atmosphärische "asthmatische" KFZ-Umwelt-Ausstoß Pt, Pd, Rh[5], mit oder ohne die ebenfalls zur Emission gelangenden aliphatischen und aromatischen Kohlenwasserstoffe sowie Rußpartikel[6-8]. - - So schneit es in Grönland seit Einführung des Katalysators bis zu 120 mal höhere Konzentrationen an Pt und Rh[9] . Die westliche Hemisphäre wird mit den Pt-gruppen-Metallen in größtem Ausmaß kontaminiert, neben der schon bestehenden Kontamination durch Hg aus fossilen Brennstoffen. - - Ein PKW mit Katalysator verliert im Schnitt 1.5 µg feinst verteiltes Pt/km Fahrt. In einem Stau mit langsamer Fahrt sind dies etwa 1.1 g. In einer Großstadt wie München werden pro Tag 1 g Pt freigesetzt oder ca.1/2 kg/Jahr plus Kohlenwasserstoffe und Rußpartikel[1-3]. - - Die direkte Einatmung durch Fußgänger sowie Schwangere und Kleinkinder erklärt die Erkrankungsraten, auch wenn anderes behauptet wird[10]. Der Mechanismus, der hier zum Tragen kommt, ist die Affinität von Ni für N und nicht für S, anders als im Falle von Hg und Cd[1-3]. Kolloidales Pt/Pd und Ni z.B. haben eine Präferenz für C, Alken, Alkin; alkylieren, katalysieren additive Reaktionen, Oxydationen, Hydrogenierungen. Pt (Cis-Pt) inhibiert oder stimuliert Proliferationen, eine IgE-Synthese, je nach Konzentration. Die Metalle können leicht in den normalen „Metall"-Haushalt (Zn, Mn, u.a.) biogenen Materials mit entsprechenden Änderungen eingreifen. - - Die Hydroxid-Radikal-Konzentration in der südlichen wie nördlichen Hemisphäre variieren signifikant seit zwei Dekaden. Das Hydroxyl-Radikal ist die dominante oxidierende Chemikalie in der Atmosphäre und damit direkt involviert in den Ozon-Haushalt und den "Treibhaus-Effekt"[11].

Radikal-Reaktionen in dieser "Metall-Sauerstoff-Stickstoff-Kohlenstoff-Wassersuppe" sind verantwortlich für das Ozon-Loch und den Treibhaus-Effekt. Die Edelmetalle und damit der KFZ-Verkehr sind für steigende Erkrankungsraten, Ozonloch, Treibhaus-Effekt, Klima-Änderung, Wasserqualität und Waldsterben "der" Verursacher und nicht Kohlendioxid mit seinem Anstieg. Neue Analyse-Methoden für die Platingruppenmetalle werden demnächst zur Verfügung stehen[12].

Literatur: [1] Kiehl, R, www.rki-i.com, pdf-files, ref. [2] Kiehl, R, BioForum 2002, 10, 618. [3] Kiehl, R, Straubinger/Landshuter Z, 17.Sept 2002. [4] Büdinger, L, Hertl, M, Allergy 2000, 55, 108-113. [5] Kiehl, R. J.Lab.Med. 2000, 24, 465-466. [6] Alastair, CL, et al, Nature 2000, 405, 7-9. [7] Science, 25 July1997, 277, News and Comment. [8] Kiehl, R, Biotech. in Bavaria 2001,1, 45-46. [9] Chem. in Britain, April 2001, p.15. [10] Hoppstock, K, Nachr.Chemie 2001, 49, 1305- 1309. [11] Prim, RG, et al, Science 2001, 0, Issue of May. [12] Kiehl, R, Int.Patent PCT/DE 02/01966.