[Frontiers in Bioscience E3, 1128-1138, June 1, 2011]

Postconditioning hormesis and the similia principle

Roeland Van Wijk[1,2], Fred A.C. Wiegant[3,4]

[1]International Institute of Biophysics, Neuss, Germany, [2]Meluna Research, Geldermalsen, The Netherlands, [3]University College, Utrecht University, The Netherlands, [4]Faculty of Science, Department of Biology, Utrecht University, The Netherlands

TABLE OF CONTENTS

1. ABSTRACT

Postexposure conditioning, as a part of hormesis, involves the application of a low dose of stress following exposure to a severe stress condition. The beneficial effect of a low level of stress in postconditioning hormesis is illustrated by a number of examples found in experimental and clinical research. Depending on whether the low-dose stress is of the same type of stress or is different from the initial high-dose stress causing the diseased state, postconditioning is classified as homologous or heterologous, respectively. In clinical homeopathy, where substances are applied according to the Similia principle, the same distinction is found between the isopathic and the 'heteropathic' or homeopathic use of low dose substances. The Similia principle implies that substances causing symptoms in healthy biological systems can be used to treat similar symptoms in diseased biological systems. Only when heterologous substances are tested for therapeutic effects, the Similia principle can be studied. It is then possible to compare the effect of treatment with the degree of similarity between the diseased state and the effects caused by different substances. The latter research was mainly performed with cells in culture using heat shocked cells post exposed to a variety of stress conditions in low dose.

2. INTRODUCTION

2.1. Hormesis

Different types of substances or conditions, for example, allergens, pathogens, ischemia, exercise, heavy metals or even psychological events may induce stress and disease. Remarkably, instead of causing a continuously linear increase or decrease in response with dose, most of these stresses seem to act in accordance with a non-linear dose-response relationship known as the biphasic response. It is characterized by a J-shaped or an inverted U-shaped dose response curve representing low dose stimulation and high dose inhibition. The biphasic dose-response pattern is termed hormesis. Historically, the phenomenon is traced back to the early 20th century. Hugo Schulz (1853-1932), a German pharmacologist, focused his research on the effects of different disinfectants on the metabolism of yeasts. He discovered that various toxic agents stimulated metabolic processes at low concentrations, while being inhibitory at higher levels. This principle of low-dose stimulation high-dose inhibition as described by Schulz became known as the Arndt-Schulz Law, representing the phenomenon of hormesis. Later, Chester Southam and John Erhlich were the first to use the term "hormesis" to describe a low-dose stimulation and high-dose inhibition of extracts from the red cider plant on the growth of various species of fungi

(1). Thomas Luckey, a pioneer researcher on radiation hormesis, initially discovered that dietary antibiotics stimulated animal growth (2,3). In the decades that followed, Luckey continued to verify the general nature of the phenomenon of hormesis (4-7). Subsequently, Edward Calabrese, a toxicologist at the University of Massachusetts, produced accumulating evidence in support of the phenomenon of hormesis (8-12).

2.2. Universality of hormesis in science

The phenomenon of hormesis has frequently been reported using different nomenclature. What these phenomena have in common is that their response relates biphasically to particular doses of stress. Such dose-response relationships are qualitatively independent of the stress-inducing agent, the endpoint measured and the system under investigation (11,13). These typical dose-response relationships are used as the Yerkes-Dodson Law in experimental psychology; the term subsidy-gradient is used in the area of ecological analysis; functional antagonism is employed nearly exclusively in enzymology; the U-shaped response, albeit applied in a wider range of disciplines, is commonly used in epidemiology; adaptive response is a term classically employed in molecular biology and physiology; biphasic response is frequently used in pharmacology; hormesis, finally, is the term that is most established in the area of toxicology. Recently, researchers from various scientific fields have agreed on the universality of the phenomena they are studying and, importantly, have agreed to use the term hormesis (12).

2.3. Preconditioning and postconditioning hormesis

The biphasic dose-response pattern is now generally thought to reflect the adaptive nature of biological systems in response to stress (13,14). Within the framework of hormesis, different approaches are used to elicit an adaptive response. Commonly, a stimulating low dose of stress is administered which initiates compensatory biological processes that confers a protective effect against exposure to a subsequent severe stress. This phenomenon is an evolutionary conserved mechanism known as *preconditioning* hormesis. Less conventional is the administration of a low dose of stress to enhance repair and recovery processes *after* exposure to a more severe stress (12,15).

In various scientific fields it has been recognized that, in addition to the protective effect of mild stress against damage from a subsequent more severe stress (i.e., preconditioning hormesis), application of a mild stress following a more severe stress condition can also confer beneficial effects (16-21). The latter phenomenon is termed *postconditioning* hormesis. 'Post' in this case refers to treatment with a low dose of stimulating stress *after* an initial treatment with a large dose of stress. The term postconditioning hormesis may be preceded by the type of inducing agent. For example, *ischemic* postconditioning hormesis which involves low doses of hypoxic stress following a myocardial infarction, or *chemical* postconditioning hormesis which involves exposure to low levels of a chemical toxicant following a previous exposure to a severe stress condition such as a heat shock or a large amount of toxic agent, etc.

2.4. Postconditiong hormesis and the homeopathic similia principle

Depending on whether the low-dose stress administered during postexposure is of the same type of stress or is different from the initial high-dose stress, postconditioning can be classified as *homologous* (i.e., the subsequent stress is the same as the initial stress) or *heterologous* (i.e., the subsequent stress is not the same as the initial stress).

Postconditioning hormesis is the main focus of this paper, and it will be discussed with reference to homeopathy and the homeopathic similia principle. It will be elucidated that the similia principle is a particular and clinically oriented application of postconditioning hormesis. In homeopathy the substances used in postconditioning are prepared in a characteristic way: following each dilution step, they are additionally succussed in a process indicated as potentization. The substances may even be potentized beyond the Avogadro number. However, even when substances are used within the molecular low-dose range, the homeopathic similia principle is highly unique. The similia principle implies that substances causing symptoms in healthy biological systems can be used to treat similar symptoms in diseased biological systems. In the homeopathic similia principle, the main vehicles used to investigate this phenomenon are heterologous rather than homologous agents. Homologous is defined as the application of a relatively diluted dose of a substance to an organism that was previously disturbed by a relatively concentrated dose of the *same* substance, also indicated as 'isopathic' application. Heterologous treatment includes a disturbance created with one substance and subsequently treated by *different* substances, also indicated as 'heteropathic' or homeopathic application. Only when heterologous substances are tested for therapeutic effects, the similia principle can be studied. It is then possible to compare the effect of treatment with the degree of similarity between the diseased state and the effects caused by different substances.

Samuel Hahnemann (1755-1843), a German physician and chemist who founded the therapeutic doctrine of homeopathy did so on the basis of the Similia principle. In 1796, Hahnemann presented his paper on "A new Principle of Healing" which he termed homeopathy (22,23). The name is derived from the Greek words homoion pathos – "similar disease." According to this therapeutic principle, there exists a similitude between the symptoms induced by the medicine and the symptoms of natural disease. From this point of view, to cure the disease, compounds or conditions associated with the occurrence of particular symptoms can be used as stimulators of intrinsic self-recovery process which then facilitates the diseased biological system to return to homeostasis (24-27). Therefore, postexposure conditioning relates primarily to this therapeutic strategy. It was Hahnemann's idea to test remedies in healthy volunteers and to note the symptoms as a way to put the similia principle into concrete practice

(28). These symptoms he then used as indications of remedies in sick people. Initially, the use of large doses as remedy were in vogue (29). When he administered his remedies to his volunteers, initially his family and students, he soon discovered that crude substances needed dilution because of toxic side-effects. Only small doses would reveal the complete action of a substance. Small doses do not imply diluted doses. Only later did reports indicate the use of diluted medications. In 1829 one finds the following statement: "In recent times (not) only small but still (rather) highly diluted and potentized drugs are used because their powers are developed most fully."(30). Hahnemann started the process of stepwise dilution and succussion. In the 6th edition of the Organon the dose recommended for proving is the 30th dilution (31). When diluting a substance, after 24 steps in a dilution ratio of 1:10 or after 12 steps in a ratio of 1:100, a dilution of one mole of starting substance would by calculation, not have any molecule of the initial substance left. This corresponds to a Hahnemannian dilution of C12 or 24X. Beyond that Avogadro boundary, statistically speaking, none of the starting material remains in the homeopathic remedy.

"Hanhnemannian" refers to the method of using a fresh vial for every step. In contrast, the same vial is used for Korsakovian potencies. Avogadro's number refers to the number of molecules in one mole (i.e., $6.023 * 10^{23}$). This fact was not known to Hahnemann. Although Hahnemann did not know for sure, he guessed that his dilution would have very little or none of the starting substance and, therefore, he called his remedies dynamization or potencies, referring to the paradoxical experience that, with his stepwise process of dilution and succussion, he observed stronger therapeutic effects than with original substances. Hahnemann's vitalistic views could have been responsible for this change. His opinion regarding succussion varied. His assertion that a drug could become potentized merely by shaking is important (32). Presumably some of his "high potencies" were not actual dilutions to a high degree but rather prepared by prolonged shaking. It is precisely homeopathy's emphasis on so-called high potencies (i.e., remedies succussed and diluted beyond Avogadro number) that creates tension with modern science because no accepted rational theory exists that could explain increased therapeutic effects with decreasing amount of the active agent, even to the point of there being no molecules of the initial agent present at all (33).

3. CLINICAL POTENTIAL OF POSTEXPOSURE CONDITIONING

Promising discoveries indicating the beneficial effects of exposing a biological system to a low recovery-enhancing dose after a severe stress condition are emerging from different scientific disciplines. The next section provides a number of examples that illustrate the clinical potential of postexposure conditioning.

3.1. Postconditioning in immunology

In immunology, particular types of adjuvants can be used to purposely infect rats thereby triggering systemic inflammation. This stress can be greatly reduced by a subsequent injection of that same adjuvant in small doses. The therapeutic effect was antigen-specific (34). The principle of (homologous) postexposure conditioning hormesis is also reflected in allergen-specific immunotherapy. This therapy is based on injecting patients suffering from allergies with increasing amounts of the offending allergen to reduce their level of sensitivity (34). For example, a case study on a patient whose milk sensitivity was repeatedly confirmed by dietary challenge, both blind and non-blind, reported sublingual milk therapy to be a successful homologous postconditioning hormesis treatment. Another study on specific immunotherapy suggested clinical benefits for allergic asthma. The double-blind placebo controlled trial indicated that immunotherapy modified the natural progression of asthma by improving lung function (35).

In patients with a chronic viral infection, therapeutic vaccination (homologous postconditioning hormesis) is aimed at modulating the host immune response to become more effective against the particular infection (i.e., reduce the level of susceptibility to the infection). Depending on the virus, chronic infection has, presumably, modulated the host immune response to become less effective against the invading virus thereby promoting viral persistence (36). It has been another area for homologous postconditioning hormesis. Already in the mid-1900's, the bacillus Calmette-Guérin (BCG) vaccine was used to treat established infection with tuberculosis (37). Other chronic viral infections that are considered possible targets for therapeutic vaccination are the hepatitis B virus (HBV), the hepatitis C virus (HCV) and human immunodeficiency virus (HIV-1) (36).

In 1985, Karpas and colleagues described the principle for HIV infected individuals receiving infusions of inactivated plasma collected from symptomless HIV infected individuals (38). Two studies, based on monthly infusions of this HIV-positive inactivated plasma demonstrated a positive clinical effect (38,39). Another study demonstrated the benefit of this treatment in a delay of the appearance of the first AIDS-defining event (40). Since the findings of Karpas and colleagues, both clinical observations and systematic trials related to homologous postconditioning hormesis have suggested a correlation between a.) the goal of the immunotherapy, that is, to decrease viral loads and increase CD4+ cell counts, and b.) the decreased morbidity and mortality resulting from HIV-1 infection (41).

3.2. Postconditioning in cardiovascular disease

Ischemic homologous postconditioning demonstrates consistent and clear cardioprotective effects in every experimentally utilized animal model (42). For example, the homologous postexposure conditioning effect of ischemia applied during early reperfusion in anesthetized open-chest dogs was cardioprotective by attenuating reperfusion injury (43). Postconditioning could be an efficient cardioprotective intervention (44-46) in patients with acute myocardial infarction submitted to primary percutaneous coronary interventions. Other studies have demonstrated that homologous postconditioning can protect the kidney from ischemia/reperfusion injury (47). Other

research has indicated that homologous postconditioning also reduces ischemic damage in the brain. However, it remains to be elucidated whether or not this type of postconditioning provides long-term protection and also improves neurological function (21).

Physical exercise is currently viewed as a potential non-pharmacological antihypertensive treatment for diet-induced obesity hypertension. In both obese and non-obese rats, hypertension, subsequent cardiac hypertrophy, myocardial fibrosis and myocardial vascularization improved in response to exercise training (48). Low exercise training also decreases blood pressure in the majority of patients with hypertension (49). The treatments are an example of heterologous postconditioning hormesis.

3.3. Postconditioning in psychological diseases

Observations of Charles Bradley in 1937 led to the paradoxical discovery that stimulating drugs such as amphetamines (benzedrine) tend to calm hyperactive children and improve their behavior. The treatment is an example of heterologous postconditioning hormesis. Owing frequently to their ameliorating (calming) effect, psychostimulants such as methylphenidate (MPH) and amphetamines, are widely used medications for treatment of ADHD in children (50).

In psychology, homologous postconditioning hormesis is recognized in exposure therapy for a wide variety of phobias. Exposure therapy is an effective means of reducing negative affective symptoms associated with different phobias (51). In recent experiments, phobic subjects experienced increased activity in the amygdala, a key brain structure implicated in fear sensation. Two weeks after exposure therapy, a significant reduction in hyperactivity at this location was recorded (52).

3.4. Postconditioning in intoxication

Application of homologous and heterologous postconditioning hormesis also appears in the field of toxicology. In an early multi-centred, double-blind study, administration of low-dose mustard gas and an extract of the plant toxin *Rhus toxicodendron* was suggested to modify local mustard-induced blistering and hasten the rate of healing (53). Recently, research suggests that exposure to sub-toxic, low-levels of toxic agents may be used to treat the effects resulting from exposure to higher doses of toxin. This may provide an alternative therapeutic approach from biological and chemical agents (16,54). Data from a cell model demonstrated the molecular basis for modulating cell's survival capacity in stress-disturbed cell cultures by application of low doses of stress conditions according to the similia principle (27,55).

4. BASIC RESEARCH

Reproducible assessment of postconditioning within a clinical framework may be difficult to realize. Application of postconditioning within a clinical context is further complicated by the narrow window within which the inducing agent initiates protective effects. Outside the therapeutic window, the postconditioning stress may become harmful. In addition, effectiveness of the agent used to induce stress may differ at the interindividual level. To study the mechanisms underlying mechanisms of postconditioning hormesis an experimental setting for accurate assessment of postconditioning hormesis is required. The advantage of experimental systems is that a diseased state can be manipulated by the dose of the inducing substance. When a diseased state is too mild, the organism recovers spontaneously at maximal speed. This offers no possibility for stimulation of recovery. When the diseased state is too severe, recovery is severely hampered. Even after application of diluted doses for curative purposes, a long experimental time may be necessary to observe stimulation of recovery. There is an important difference between the spontaneous clinical disease and induced disease in fundamental studies. In the spontaneous clinical situation, normal recovery is usually blocked. With the potential therapeutic substance, the doctor aims to unblock the healing mechanism. Experimentally induced diseases are recoverable, unless the recovery mechanism is damaged or disturbed. One can argue that an intermediate diseased state with highly significant clinical parameters can be used to study effects. Examples of such parameters are survival (for intact organisms) and cell viability (for *in vitro* cultured cells).

4.1. HomBRex database

A review on basic research regarding homologous and heterologous postconditioning hormesis may be based on the HomBRex database (56-58). The HomBRex database deals specifically with basic research experiments in the field of homeopathy indexed studies using biological systems including animal, human, plant, fungi and microbial organisms. The main objective of this database is to index proving and therapeutic experiments on the Similia Principle and the role of dilution and succussion of substances in experimental biological systems. The establishment of the HomBRex Database on Fundamental Homeopathy Research and analysis of the collection has been described elsewhere (http:// www.carstens-stiftung.de/hombrex). This archive is continuously updated by systematically searching bibliographic databases and screening for duplications. In 2008, the database provided information on 1300 experiments. These experiments were divided into 'ídeal' model proving, prophylactic and therapeutic experiments. In the latter experiments, an effect of a substance was tested in a diseased or disturbed system.

An extraordinary diversity of model systems has been examined in fundamental homeopathy research. The research database includes investigations of biological systems ranging from complex, multicellular organisms (i.e., mammals and plants) to single cell organisms and from intact organisms to isolated cells and subcellular structures. The majority of experiments were carried out on animals: the second largest group is with plants. Complex, multicellular organisms (animal, human and plant systems) were tested as whole or parts of systems either after isolation or *in vitro* culturing (e.g., as isolated organs or cultured cells). The data demonstrate an overwhelming variety in biological systems, diseased states and substances. The majority of experiments with animals and

plants were with intact organisms. In experiments with animals or part of animals, the favorite animals were rats and mice. A large number of substances were used for therapeutic postconditioning purposes including high and low dilutions and potencies.

4.2. Studies on intact rats

The intact rat is the biological system most utilized in basic science homeopathic research. It was recently selected to study the Similia Principle utilizing the HomBRex database. The database was analyzed for basic therapeutic experiments with diseased intact rats and the administration of a substance with a therapeutic intention, both homologous and heterologous treatments of disease states (59). Several diseased states and substances utilized for induction of these states were registered in 67 experiments; intoxication was the major induced state. In 40 experiments, the effects of treatments were measured at the level of the whole organism. The parameters that characterize the effect of substances at the levels of the entire rat are highly specific to the diseased state. In intoxicated rats, excretion of a toxin was one frequently used parameter. Specific behavioral disturbances, edema and inflammation were also frequently recorded. Rats with cancer, diabetes, other hormonal disturbances, arthritis, ulcer, organ enlargement, wound healing and itching were studied less frequently. In 27 experiments, the effect of a therapeutic substance was studied in isolated organs. The major organs in the intoxication studies were liver and blood. Changes in liver were characterized by histology and enzyme activity.

Four types of diseased states were analyzed in greater depth: intoxication, behavioral disturbances, edema/inflammation and hormonal disturbances. The objective was to compare the nature of the pretreatment and the substances used for therapeutic purpose. The data make it possible to distinguish, for each diseased state, homologous and heterologous applications of the therapeutic substance to evaluate both the isopathic and the heteropathic approach, respectively. The major compounds used for intoxication are arsenite, carbon chloride and lead. In arsenite intoxication, almost all treatments are homologous. In contrast, in carbon tetrachloride intoxication, rats were treated in a heterologous fashion. Rats intoxicated with lead were treated in both homologous and heterologous fashion. A few intoxications were studied in only a single experiment. In the single study on bee venom, the treatment was homologous, for bromobenzene it was heterologous. Gentamycin intoxication was treated both in a homologous and heterologous manner. The major behavioral disturbances are ethanol addition, motility dysfunction after strychnine and hexobarbital exposure, disturbed oculomotor reflexes and hyperactivity following excess caffeine. A few other behavioral disturbances were only studied in a single experiment. Oculomotor reflexes were treated in a homologous fashion, whereas ethanol addiction and motility dysfunction were treated only in a heterologous way. Both homologous and heterologous treatments were used in hyperactivity after caffeine exposure. Edema and inflammation were induced by different treatments and in most experiments these conditions were treated in a heterologous manner. Likewise, the treatments in the studies on ovariectomy or hormonal disturbances were mostly of the heterologous type. Overall, both low and high potencies were used. In addition, a potency range was tested in many experiments (59).

For both homeopathy-oriented and modern postconditioning hormesis oriented researchers, this dataset is of interest for its potential to unravel the mechanisms. The selected group of experiments can be further used to analyze and evaluate treatment effects. Researchers will then also be able to address the following questions: “Why was a particular substance selected?” and “Is treatment based on proving data and substance specificity?” With these data, it should be possible to document more evidence to enhance the understanding and therapeutic use of the similia principle in the general science of medicine. However, it must be noted that full evaluation of the similia principle requires more than evaluating the effect of the homologous (isopathic) approach and more than a heterologous treatment. The similia principle implies that the heterologous substances are *effective* remedies only if they trigger similar symptoms when applied to healthy biological systems. Therefore, the study of the similar principle requires a comparison between heterologous different substances with respect to both therapeutic effects and the similarity of symptom patterns they induce in healthy systems. This is discussed in the next paragraph utilizing cultured cells as biological model.

4.3. Studies on cultured cells

The research on postconditioning hormesis has been carried out with cells isolated originally from the well-differentiated hepatoma Reuber H35. The cultured Reuber H35 rat hepatoma cells have proven to be a stable cell line from which many characteristics have been described (60). In the research, both a harmful physical (heat shock) and several chemical stressors were used. Cells were exposed to different strengths of stress by varying dose and time in order to select the harmful (high dose) and subsequent postconditioning hormetic (low dose) effects. The stress condition was carefully selected in order to prevent the occurrence of much irreversible damage or compromised resilience ability. For an experimental protocol, stressed cells should be able to express their recovery- and survival capacities as well as allow a further increase by changes in environmental circumstances. Only then, an addition in survival capacity in response to a subsequent exposure to a low dose postconditioning treatment can be achieved. A final harmful test stress exposure is used to record the possible increase in cell’s survival capacity (27,55). The present paragraph also describes a molecular biology approach to the field of postconditioning hormesis utilizing stressed “*in vitro*” cultured cells. It focuses on: a.) the proteotoxic response of cells and b.) the regulation of heat shock (stress) protein (hsp) synthesis. Proteotoxicity, originally defined by Hightower (61) to indicate the detrimental action of denatured proteins in cells, is a phenomenon of increasing interest in biomedical disciplines. Damage to cellular proteins occurs: a.) after heat shock, b.) after ingestion of environmental pollutants such as heavy

metals, and c.) following ischemia. The damage incurred is frequently due to reactive oxygen species (oxidative stress). Denatured proteins are increasingly recognised as crucial factors in the development of various chronic diseases including neurodegenerative, atherosclerotic, diabetic, etc. and in the process of aging (62-67). To limit proteotoxicity an automatic set of hsp's (chaperones) are produced that are involved in cellular repair, recovery and defence mechanisms. Bacteria and eukaryotes defend against misfolded ("toxic") protein aggregation utilizing two protein types: molecular chaperones (typically hsp27, hsp60, hsp70, hsp90 and hsp100) and the ATP-dependent proteases (including the 26S proteasome) (68). It has since been demonstrated that chaperones possess many active functions: they repair structural damages by forcefully disentangle aggregated proteins, unfold and refold them into 're-educated and born again' functional proteins (68,69). The various hsp's appear to be differentially induced depending on the stress condition (70,71). With this framework in mind, the question was raised regarding the possible stimulating effect of the postconditioning hormetic treatment on the stress protein response. The next paragraphs will first focus on homologous and then on heterologous postexposure conditioning using chemical (arsenite and cadmium) and physical (heat) stress conditions.

4.3.1. Homologous postconditioning hormesis with arsenite

To study homologous arsenite postconditioning, studies were carried out with cells that were exposed for 1 h to either 100 or 300 μM arsenite (17). The data demonstrated that postconditioning treatment (1, 3 or 10 μM) increased survival capacity compared to cells that were only pretreated with 100 or 300 μM. However, the stimulation was dependent on the pre-exposure. A larger stimulation was observed when increasing low doses of 1, 3 and 10 μM followed pre-exposure of 100 μM arsenite. In contrast, cells pre-exposed to 300 μM arsenite only demonstrated an enhancement in the presence of 1 and 3 μM; 10 μM was detrimental. Effects of these low concentrations could not be observed in non pre-exposed cells. The effect of postconditioning arsenite treatment on the production of stress proteins was also evaluated (17). When a treatment with 100 μM arsenite was followed by incubation under control conditions (arsenite-free medium), synthesis of the hsp60, 68, 70, 84, and 100 could be observed. The synthesis of most of these stress proteins reached a maximum 3 hr after the start of the exposure to arsenite. When, however, the pretreatment was followed by continuous postconditioning incubation with low concentrations of arsenite, an enhancement of the synthesis of stress proteins was observed. Since the treatment with 3 or 10 μM arsenite alone (without pretreatment) did not cause any induction of stress proteins, it was concluded that small doses of arsenite enhance the relative synthesis of stress proteins.

4.3.2. Homologous postconditioning hormesis with cadmium.

To study homologous cadmium postconditioning, cells were exposed for 1 h to either 10 or 30 μM cadmium (20). In addition, the effect of small dose treatments on cell cultures with different initial exposures of cadmium was studied. Following exposure to 10 or 30 μM cadmium, the cultures were subsequently incubated utilizing a range of lower concentrations of cadmium (up to 1 μM) for 10 h. The data demonstrated that lower concentrations of cadmium (ranging from 0.03 to 1 μM) increased survival capacity in cells that were pre-exposed for 1 h to 10 μM. No effect of these low concentrations was observed on survival capacity in non-pre-exposed cells. When cells were pre-exposed to 30μM cadmium, survival capacity increased only when cultures were exposed postconditionally with low concentrations of up to 0.1 μM. Higher postconditioning concentrations of cadmium (0.3, 0.6 or 1.0 μM) resulted in an inhibition of the development of survival capacity. Thus, it was again demonstrated that small-dose enhancement of survival capacity is a function of the initial condition of the cadmium-exposed cells. In addition, a small dose of cadmium applied postconditionally was able to enhance the synthesis of stress proteins in pre-treated cells. Previous data on specific stress protein synthesis demonstrated a transient increase in synthesis of all stress proteins (hsp28, hsp32, hsp68, hsp70, hsp84, and hsp100) when cells were pretreated with 10 μM cadmium followed by incubation in a cadmium-free medium (71). When similarly pretreated cells were incubated in media containing a low concentration of cadmium (0.3 μM), an enhanced and prolonged induction of several stress proteins was observed (74).

4.3.3. Homologous postconditioning hormesis with heat-shock

To study post-heat conditioning hormesis, cells were initially exposed for 30 min at either 42°C or 43.5°C and postconditionally incubated at mild (fever-like) temperatures (38-41°C). These mild postconditioning fever-like temperatures appeared to be beneficial following the 42°C heat treatment whereas they depressed the survival capacity of cells if they were pre-exposed to 43.5°C treatment. Interestingly, the exposure of untreated cells to 40°C for 6 hours was without effect on survival capacity (19). Schamhart and coworkers were the first to study whether the synthesis of specific stress proteins (hsp28, hsp60, hsp68, hsp70, hsp84 and hsp100) induced by a 30 min heat shock at 42°C was influenced upon post-conditioning exposure to a lower hyperthermic temperature. The homologous postconditioning caused a significant induction (72). Similar observations were reported for mRNA levels of hsp68 and hsp84 when heat shocked cells were post-exposed to 40°C and 41°C (19). These observations were further supported by the observation of Delpino *et al* (73) who demonstrated an enhanced synthesis of stress proteins and an enhanced survival capacity when the initial heat shock was followed by a lower hyperthermic temperature.

4.4. Heterologous postconditioning hormesis: Towards the similia principle

4.4.1. Methodological aspects

In homeopathy, the selection of a remedy is based on the overall symptom pattern of the patient and includes subjective and objective symptoms. However, not all symptoms are equally important. A symptom like

headache, for example, is too general to be of any value. Likewise in a cell model not all changes in cell structure, metabolism and physiology observed following stress exposure are useful 'symptoms'. A change in cell morphology for instance is, like headache, rather general. In contrast, the pattern of induced stress proteins is more specific and has been selected in research as molecular symptoms at the cellular level, to analyze the specificity of the similia principle. The pattern of induced stress proteins (both heat shock proteins [hsps] and glucose-regulated proteins [grps]) was considered the sole indication to direct research as to the choice of the low dose agent. The next question relates to the specificity of the stimulation of survival capacity and of hsp synthesis. Related to this question is the utilization of a protocol in which damaging stress conditions were followed by exposure to a smaller dose of different stress condition treatments (74-76). The stress conditions differ in stressor-specific induction of stress proteins (71).

The stress conditions used for post-exposure purposes included arsenite, several heavy metal ions (cadmium, mercury, lead and copper), two different oxidative stress conditions (menadion and diethyldithiocarbamate) and a mild hyperthermic temperature. These stress conditions differ both in the extent as well as the pattern in which various stress proteins are stimulated. The qualitative specificity, for instance, shows that lead induces the grps (grp78/grp94), which are not induced by heat shock, other heavy metals or oxidative stressors. Only arsenite induces grp94 slightly. Heat shock and arsenite induce hsp60, whereas cadmium and diethyldithiocarbamate do not.

4.4.2. Remedy picture and similarity

Based on the differences between stress induced protein patterns, one particular condition corresponding with a particular pattern can be taken as standard; all the other conditions and patterns can then be compared to this. In the study heat shock was selected as the standard condition and the similarity between response patterns was estimated based on the major hsps (hsp28, 32, 60, 68, 70, 84, 100) and on the major grps (grp78 and 94). Analogous to the symptoms that an agent is able to induce in healthy biological systems, the stressor-specific patterns of induced proteins can be considered 'remedy pictures' at the cellular level. The ability to quantify the 'overlap' between disease picture and remedy picture, a crucial prerequisite to study the similia principle, has now been met. The specificity of low dose stimulation on cell survival capacity was evaluated by analyzing the effect of a range of mild stress conditions that were used postconditionally following a heat shock (76). A heat shock was selected (42°C for 30 min) that was not substantially affecting actual cell survival but was able to stimulate sub-optimal development of cell survival capacity.

4.4.3. Similia principle tested

To select the small dose treatment, conditions were established that were just below the limit of having an effect on survival capacity as well as on the synthesis of stress proteins during an 8 h time period. When the various small dose stressors were applied after an initial heat shock, an increase in survival capacity was observed. This increase was labelled "survival stimulation factor" (the ratio of relative survival with low dose postconditoning versus the effect on survival due to the initial heat shock only). It represents the degree of stimulation of survival capacity as exerted by postconditioning with the low doses. However, the increase appeared to depend on the nature of the low dose stressor. Heterologous postconditioning demonstrated an increase of the "survival stimulation factor" but not as much as homologous postconditioning. The stimulation of survival capacity was correlated with the degree of similarity between the stress protein pattern induced by heat shock and the pattern of stress protein induction characteristic (specific) for the compounds that were applied in small doses. The survival stimulation factor plotted against the degree of similarity demonstrated a highly significant correlation. It was concluded that, in general, a higher percentage of similarity in stress protein induction pattern predicts a higher stimulation of survival capacity (76).

4.4.4. Molecular aspects

To explain the variability of small dose stimulatory action on heat-shocked cells, it was hypothesized that such conditions only induce an increased survival if they are able to stimulate the specific endogenous defense and recuperative mechanisms required by damaged cells. Since stress proteins are viewed as a reflection of the initiation of endogenous defense at the molecular level, the research evaluated whether observed differences in stimulation by small doses were related to the specificity in the overall pattern of stress proteins. Indeed, a significant correlation was observed for most stress proteins between enhanced additional synthesis due to low dose stress and the degree of similarity between the induction of individual hsps by high and low dose stress conditions (76). It was also concluded that during the period of enhanced sensitivity, cells react to substances applied in low dose, to which they would normally not react, and that the stimulation of recovery processes depends on the similarity in effect between high dose and low dose stress condition.

In summary, the degree of stimulation appears to be stressor-specific. The specificity is not only present in the development of the survival capacity, but also in the subsequent enhancement of the heat shock induced synthesis of stress proteins. The degree of stimulation of survival capacity by sequential postconditoning exposure to low doses of the mentioned stressors is determined by the degree of stress protein pattern similarity between the stress condition used as a low dose and the initial high dose pre-exposure condition. This observation supports the validity of the similia principle at the cellular level.

5. DISCUSSION AND CONCLUSION

The generally accepted concept and evolutionary conserved phenomenon of hormesis involving both low-dose stimulation and high-dose inhibition has been studied over decades in many fields. Initially, hormesis had only been identified with preexposure conditioning. Postexposure conditioning has only recently arrived in the field of hormesis and has, therefore, not yet reached a comparable level of acceptance in the scientific world. Postconditioning hormesis involves administration of a low

dose of stress following exposure to a severe stress. The initial severe stress affects the homeostatic (balanced) state of a biological system and activates intrinsic self-recovery mechanisms. Administration of a subsequent low dose stress may modulate or over-activate these recovery mechanisms. Activation of these adaptation strategies with a low dose stress can confer beneficial effects to the biological system. Promising results indicating the beneficial effects of postexposure conditioning are emerging from different scientific disciplines. This paper presents a number of such reports from current clinical research illustrating the relevance and therapeutic potential of postconditioning hormesis.

To study the mechanisms underlying mechanisms of postconditioning hormesis an experimental setting is required. The advantage of experimental systems is that a diseased state can be manipulated by the dose of the inducing substance. For such study, the HomBRex database has been developed (56-58). The database deals specifically with homeopathic proving and therapeutic experiments as well as with the use of dilutions and succussions in experimental biological systems. In the therapeutic experiments, an effect of a low dose substance was tested in a diseased or disturbed system. The research includes investigations of biological systems ranging from complex, multicellular organisms (i.e., mammals and plants) to single cell organisms and from intact organisms to isolated cells and subcellular structures. An extraordinary diversity of model systems has been examined in fundamental homeopathy research. The intact rat is the biological system most utilized in basic science homeopathic research. It was recently selected to study the homologous and heterologous low doses treatments of disease states (59). Intoxication, behavioral disturbances, edema, inflammation and less frequently, rats with cancer, diabetes, hormonal disturbances, arthritis, ulcer, organ enlargement, wound healing and itching have been studied. The data make it possible to distinguish, for each diseased state, homologous and heterologous applications (both low and high potencies) of the therapeutic substance to evaluate both isopathic and homeopathic treatments. For both homeopathy-oriented and modern postconditioning hormesis oriented researchers, this dataset is of interest for its potential to unravel the underlying mechanisms. This group of experiments can be further analyzed to evaluate treatment effects.

A full evaluation of the similia principle requires more than demonstrating a beneficial effect of an isopathic (or homologous) treatment and more than that of a heterologous treatment. The similia principle implies that the heterologous substances used for postconditioning purposes are *effective* remedies only if they trigger similar symptoms when applied to healthy biological systems. Therefore, the study of the similar principle requires a comparison between many different heterologous substances with respect to both therapeutic effects and the similarity of symptom patterns they induce in healthy systems. This approach has been systematically studied utilizing cultured cells as a biological model (27,55,76). The data support the hypothesis that small doses of toxic compounds may, under certain conditions, have beneficial effects related to stimulation of endogenous cytoprotective mechanisms. It is of interest that this stimulatory effect of small doses is dependent on the initial exposure condition. The more severe the initial stress conditions, the smaller the concentration required for stimulating survival and hsp induction. However, small doses can unexpectedly merge into a harmful range, especially when the initial stress condition has been severe. These observations in the framework of homologous postconditioning are in agreement with the "Law of Initial Values" formulated by Wilder (77,78). This law states that the response of a (cellular) function to any (outside) agent depends to a large degree on the "initial level" of that function at the start of the experiment. According to this law, the higher the initial postconditioning stimulus, the smaller the response is to a "function-raising" substance, and the greater the response is to "function-depressing" agents. Conversely, the lower the "initial level", the greater is the response to 'function-raising' agents and the lesser to function-depressing ones.

Agutter (13) raised the question as to how the toxic effect of the stressor can be ameliorated by subsequent exposure to a low dose of the same stressor. Although mechanistic explanations of hormesis have been suggested during the past few years (13,14,79), the beneficial effect of low dose stress, is experimentally best explained by the proteotoxicity and stress protein response defense system (80). Postexposure of heat-shocked cells to different chemical low-dose stress conditions demonstrated a differential stimulation of both survival capacity development and of heat shock protein synthesis. The degree of stimulation appeared to depend on the similarity of both the molecular and cellular effects of the stress conditions used as initial disturbance and the postexposure treatment.

It is suggested that the discovery of Hahnemann's *similia similibus curentur* ('let like be cured by like') is still worth-while in the twenty-first century. In this respect the comparative research on the relation between postconditioning hormesis and the homeopathic Similia principle is an interesting challenge for 'bridge-builders' between science and homeopathy.

6. REFERENCES

1. CM Southam, J Erhlich, Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture. *Phytopathol* 33, 517-524 (1943)

2. PR Moore, TD Luckey, E McCoy, CA Elvehjem, EB Hart. Use of sulfasuxadine, streptothrycin and streptomycin in nutritional studies with the chick. *J Biol Chem* 165, 437-441 (1946)

3. TD Luckey. Antibiotics in nutrition. In: Antibiotics, Their Chemistry and Non-Medical Uses. Ed: HS Goldberg. Van Nostrand New York, 174-321 (1959)

4. TD Luckey. Hormology in nutrition. *Science* 132, 1891-1893 (1960)

5. TD Luckey. Insecticide hormoligosis. *J Econ Entomol* 61, 7-12 (1968)

6. TD Luckey. Ionizing radiation promotes protozoan reproduction. *Rad Res* 108, 215-221 (1986)

7. JF Townsend, TD Luckey. Hormoligosis in pharmacology. *J Am Med Assoc* 173, 44–48 (1960)

8. EJ Calabrese. Converging concepts: Adaptive response, preconditioning, and the Yerkes-Dodson law are manifestations of hormesis. *Ageing Res Rev* 7, 8-20 (2008)

9. EJ Calabrese, LA Baldwin. Hormesis as a biological hypothesis. *Env Health Persp* 106, 357-362 (1998)

10. EJ Calabrese, LA Baldwin. Applications of hormesis in toxicology, risk assessment and chemotherapeutics. *Trends Pharm Sci* 23, 331-337 (2002)

11. EJ Calabrese, LA Baldwin. Hormesis: the dose-response revolution. *Annu Rev Pharmacol Toxicol* 43, 175-197 (2003)

12. EJ Calabrese, KA Bachmann, AJ Bailer, PM Bolger, J Borak, L Cai, N Cedergreen, MG Cherian, CC Chiueh, TW Clarkson, RR Cook, DM Diamond, DJ Doolittle, MA Dorato, SO Duke, L Feinendegen, DE Gardner, RW Hart, KL Hastings, AW Hayes, GR Hoffmann, JA Ives, Z Jaworowski, TE Johnson, WB Jonas, NE Kaminski, JG Keller, JE Klaunig, TB Knudsen, WJ Kozumbo, T Lettieri, S-Z Liu, A Maisseu, KI Maynard, EJ Masoro, RO McClellan, HM Mehendale, C Mothersill, DB Newlin, HN Nigg, FW Oehme, RF Phalen, MA Philbert, SIS Rattan, JE Riviere, J Rodricks, RM Sapolsky, BR Scott, C Seymour, DA Sinclair, J Smith-Sonneborn, ET Snow, L Spear, DE Stevenson, Y Thomas, M Tubiana, GM Williams, MP Mattson. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework. *Toxicol Appl Pharmacol* 222, 122–128 (2007)

13. PS Agutter. Elucidating the mechanism(s) of hormesis at the cellular level: the universal cell response. *Am J Pharmacol Toxicol* 3, 97-107 (2008)

14. MP Mattson. Hormesis and disease resistance: activation of cellular stress response pathways. *Hum Exp Toxicol* 27, 155-162 (2008)

15. EJ Calabrese. Hormesis: Why is it important to toxicology and toxicologists. *Env Toxicol Chem* 27, 1451-1474 (2008)

16. WB Jonas, JA Ives. Should we explore the clinical utility of hormesis? *Hum Exp Toxicol* 27, 123-127 (2008)

17. JH Ovelgönne, FAC Wiegant, JEM Souren, J Van Rijn, R Van Wijk. Enhancement of the stress response by low concentrations of arsenite in arsenite-pretreated H35 hepatoma cells. *Toxicol Appl Pharmacol* 132, 146-155 (1995)

18. R Van Wijk, H Ooms, FAC Wiegant, JEM Souren, JH Ovelgönne, JM Van Aken, AWJM Bol. A molecular basis for understanding the benefits from subharmful doses of toxicants. *Environmental Management and Health* 5, 13-25 (1994)

19. R Van Wijk, JH Ovelgönne, E de Koning, K Jaarsveld, J Van Rijn, FAC Wiegant. Mild step-down heating causes increased transcription levels of hsp68 and hsp84 mRNA and enhances thermotolerance development in Reuber H35 hepatoma cells. *Int J Hyperth* 10, 115-125 (1994)

20. FAC Wiegant, J Van Rijn, R Van Wijk. Enhancement of the stress response by minute amounts of cadmium in sensitized Reuber H35 hepatoma cells. *Toxicol* 116, 27-37 (1997)

21. H Zhao. The protective effect of ischemic postconditioning against ischemic injury: from the heart to the brain. *J Neuroimmune Pharmacol* 2, 313-318 (2007)

22. JM Schmidt. The Publications of Samuel Hahnemann (in German]. *Sudhoffs Archiv* 72, 14-36 (1988)

23. JM Schmidt. History and relevance of the 6th edition of the Organon of Medicine (1842). *Br Homeopathic J* 83, 42-48 (1994)

24. S Hahnemann Lesser Medical Writings. Haug, Heidelberg (1971) (original: Arnold, Dresden 1929)

25. S Hahnemann. Organon of Healing. Vol 6. Hippocrates, Stuttgart (1979)

26. S Hahnemann. Organon of Medicine. JP Tarcher, Los Angeles (1982)

27. R Van Wijk, FAC Wiegant. The Simila Principle. An Experimental Approach on the Cornerstone of Homeopathy. Karl und Veronica Carstens-Stiftung, Essen (2006)

28. R Jütte. 200 years of [the] similarity principle: Magic, medicine, metaphor. *Allgemeine Homöopathische Zeitung* 242: 3-16 (1997)

29. S Hahnemann. Organon (1st Ed) Paragraph 63. Köthen (1810)

30. S Hahnemann. Organon (4th Ed) Paragraph 121. Arnold, Dresden, Leipzig (1829)

31. S Hahnemann. Organon (6th Ed) Paragraph 128. Schwabe, Leipzig (1921) and Boehricke and Tafel, Philadelphia (1922)

32. S Hahnemann. Organon (5th Ed) Paragraph 270. Arnold, Dresden, Leipzig (1833)

33. H Walach, WB Jonas, J Ives, R Van Wijk, O Weingartner. Research on homeopathy: state of the art. *J Altern Complem Med* 11, 813-829 (2005)

34. P Bellavite, R Ortolani, A Conforti. Immunology and homeopathy. 3. Experimental studies on animal models. *eCAM* 3, 171-186 (2006)

35. J Wang. Allergy immunotherapy as an early intervention in patients with child-onset atopic asthma. *Pediatrics* 120, S148-S149 (2007)

36. M Sällberg, M Weiland, L Frelin. Therapeutic vaccines: challenges of chronic viral infections. *Drug Disc Today: Therap Strateg* 4, 253-266 (2007)

37. SA Plotkin. Vaccination against the major infectious diseases. *C R Acad Sci III* 322, 943-951 (1999)

38. A Karpas W Gillson, PC Bevan, JK Oates. Lytic infection by British AIDS virus and development of rapid cell test for antiviral antibodies. *Lancet* 2(8457), 695-697 (1985)

39. GG Jackson, JT Perkins, M Rubenis, DA Paul, M Knigge, JC Despotes, P Spencer. Passive immunoneutralization of human immunodeficiency virus in patients with advanced AIDS. *Lancet* 2(8612), 647-652 (1988)

40. D Vittecoq, S Chevret, L Morand-Joubert, F Heshmati, F Audat, M Bary, T Dusautoir, A Bismuth, JP Viard, F Barré-Sinoussi. Passive immunotherapy in AIDS: a double-blind randomized study based on transfusions of plasma rich in anti-human immunodeficiency virus 1 antibodies vs. transfusions of seronegative plasma. *Proc Natl Acad Sci USA* 92, 1195-1199 (1995)

41. NC Connolly, TL Whiteside, S Wilson, V Kondragunta, CR Rinaldo, SA Riddler. Therapeutic immunization with human immunodeficiency virus type 1 (HIV-1) peptide-loaded dendritic cells is safe and induces immunogenicity in HIV-1-infected individuals. *Clin Vaccine Immunol* 15, 284-292 (2008)

42. DA Liem, HM Honda, J Zhang, D Woo, P Ping. Past and present course of cardioprotection against ischemia-reperfusion injury. *J Appl Physiol* 103, 2129-2136 (2007)

43. ZQ Zhao, JS Corvera, ME Halkos, F Kerendi, NP Wang, RA Guyton, J Vinten-Johansen. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol* 285, H579-H588 (2003)

44. CE Darling, PB Solari, CS Smith, MI Furman, K Przyklenk. Postconditioning the human heart: Multiple balloon inflations during primary angioplasty may confer cardioprotection. *Basic Res Cardiol* 102, 274-278 (2007)

45. WK Laskey. Brief repetitive balloon occlusions enhance reperfusion during percutaneous coronary intervention for acute myocardial infarction: a pilot study. *Catheter Cardiovasc Interv* 65, 361-367 (2005)

46. P Staat, G Rioufol, C Piot, Y Cottin, TT Cung, I L'Huillier, JF Aupetit, E Bonnefoy, G Finet, X André-Fouët, M Ovize. Postconditioning the human heart. *Circulation* 112, 2143-2148 (2005)

47. G Serviddio, AD Romano, L Gesualdo, R Tamborra, AM Di Palma, T Rollo, E Altomare, G Vendemiale. Postconditioning is an effective strategy to reduce renal ischemia/reperfusion injury. *Nephrol Dial Transpl* 23, 1504-1512 (2008)

48. AR Pinheiro, AR Cunha, MB Aguila, CA Mandarim-de-Lacerda. Beneficial effects of physical exercise on hypertension and cardiovascular adverse remodeling of diet-induced obese rats. *Nutr Metab Cardiovasc Res* 17, 365-375 (2007)

49. JM Hagberg, J-J Park, MD Brown. The role of exercise training in the treatment of hypertension: an update. *Sports Med* 30, 193-206 (2000)

50. RL Findling. Evolution of the treatment of attention-deficit/hyperactivity disorder in children: A review. *Clin Therap* 30, 942-957 (2008)

51. BO Rothbaum, AC Schwartz. Exposure therapy for posttraumatic stress disorder. *Am J Psychother* 56, 59-75 (2002)

52. L Goossens, S Sunaert, R Peeters, EJL Griez, KRJ Schruers. Amygdala hyperfunction in phobic fear normalizes after exposure. *Biol Psych* 62, 1119-1125 (2007)

53. J Paterson. Report on mustard gas experiments. *J Am Homoeop Assoc* 37, 47-50 / 37, 88-89 (1944)

54. AL Szeto, F Rollwagen, WB Jonas. Rapid induction of protective tolerance to potential terrorist agents: a systematic review of low- and ultra-low dose research. *Homeopathy* 93, 173-178 (2004)

55. FAC Wiegant, R Van Wijk. The similia principle; results obtained in a cellular model system. *Homeopathy* 99, 3-14 (2010)

56. H Albrecht, R Van Wijk, S Dittloff. A new database on basic research in homeopathy. *Homeopathy* 91, 162-165 (2002)

57. R Van Wijk, H Albrecht. Classification of systems and methods used in biological research in homeopathy. *Homeopathy* 96: 247-251 (2007)

58. R Van Wijk, H Albrecht. Proving and therapeutic experiments in the HomBRex basic homeopathy research database. *Homeopathy* 96: 252-257 (2007)

59. R Van Wijk, J Clausen, H Albrecht. The rat in basic therapeutic research in homeopathy. *Homeopathy* 98: 280-286 (2009)

60. R Van Wijk. Regulation of DNA synthesis in cultured rat hepatoma cells. *Int Rev Cytol* 85, 63-107 (1983)

61. LE Hightower. Heat shock, stress proteins, chaperones, and proteotoxicity. *Cell* 66, 191-197 (1991)

62. SK Calderwood, A Murshid, T Prince. The shock of aging: Molecular chaperones and the heat shock response in longevity and aging. *Gerontology* 55, 550-558 (2009)

63. E Cohen, A Dillin. The insulin paradox: aging, proteotoxicity and neurodegeneration. *Nat Rev Neurosci* 9, 759-767 (2008)

64. N Gregersen, P Bross, S Vang, JH Christensen. Protein misfolding and human disease. *Annu Rev Genomics Hum Genet* 7, 103-124 (2006)

65. M Liu, I Hodish, CJ Rhodes, P Arvan. Proinsulin maturation, misfolding, and proteotoxicity. *Proc Natl Acad Sci USA* 104, 15841-15846 (2007)

66. RI Morimoto. Proteotoxic stress and inducible chaperone networks in neurodegenerative disease and aging. *Genes Dev* 22, 1427-1438 (2008)

67. R Van Wijk, EPA Van Wijk, FAC Wiegant, J Ives. Free radicals and low-level photon emission in human pathogenesis: state of the art. *Ind J Exp Biol* 46, 273-309 (2008)

68. RJ Ellis. Protein misassembly: macromolecular crowding and molecular chaperones. In: Molecular Aspects of the Stress Response: Chaperones, Membranes and Networks. Eds: P Csermely, L Vigh. Landes Bioscience and Springer Science and Business Media, New York, 1-13 (2007)

69. P Csermely, L Vigh. Molecular Aspects of the Stress Response: Chaperones, Membranes and Networks. Landes Bioscience and Springer Science and Business Media, New York (2007)

70. JA Ryan, LE Hightower. Stress proteins as molecular biomarkers for environmental toxicology. *EXS* 77, 411-424 (1996)

71. FAC Wiegant, JEM Souren, J Van Rijn, R Van Wijk. Stressor-specific induction of heat shock proteins in rat hepatoma cells. *Toxicol* 94, 143-159 (1994)

72. DHJ Schamhart, G Zoutewelle, H Van Aken, R Van Wijk. Effects on the expression of heat shock proteins by step-down heating and hypothermia in rat hepatoma cells with a different degree of heat sensitivity. *Int J Hyperthermia* 8, 701-716 (1992)

73. A Delpino, FP Gentile, F Di Modugno, M Benassi, AM Mileo, E Mattei. Thermo-sensitization, heat shock protein synthesis and development of thermotolerance in M-14 human tumor cells subjected to step-down heating. *Radiat Environ Biophys* 31, 323-332 (1992)

74. FAC Wiegant, J Van Rijn, R Van Wijk. Enhancement of the stress response by minute amounts of cadmium in sensitized Reuber H35 hepatoma cells. *Toxicol* 116, 27-37 (1997)

75. FAC Wiegant, N Spieker, R Van Wijk. Stressor-specific enhancement of hsp induction by low doses of stressors in conditions of self- and cross-sensitization. *Toxicol* 127, 107-119 (1998)

76. FAC Wiegant, JEM Souren, R Van Wijk. Stimulation of survival capacity in heat-shocked cells by subsequent exposure to minute amounts of chemical stressors: Role of similarity in hsp-inducing effects. *Hum Exp Toxicol* 18, 460-470 (1999)

77. J Wilder. The law of initial value in neurology and psychiatry; facts and problems. *J Nerv Ment Dis* 125, 73-86 (1957)

78. J Wilder. Stimulus and response; the law of the initial value. Wright, Bristol (1967)

79. ARD Stebbing. A mechanism for hormesis - a problem in the wrong discipline. *CritRevToxicol* 33, 463-467 (2003)

80. R Van Wijk, FAC Wiegant. Postconditioning hormesis and the homeopathic similia principle: molecular aspects. *Human Exp Toxicol* 29, 561-565 (2010)

Key Words: Hormesis, Postconditioning, Homeopathy, Similia principle, Review

Send correspondence to: Roeland Van Wijk, Koppelsedijk 1a, 4191 LC Geldermalsen, Netherlands, Tel: 31345-570110, Fax: 31345-570110, E-mail: meluna.wijk@wxs.nl

http://www.bioscience.org/current/volE3.htm