The Working Mechanisms of Antihomotoxic Potentized Preparations

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Abstract

Antihomotoxic combination preparations intervene in cell language on the cytokine level. Transforming growth factor beta (TGF-β) and the cytokine-dependent nuclear transcription factor kappa B (NF-κB) play central roles in this process. TGF-β is the extracellular switch in maintaining the balance between fibrogenesis and fibrolysis; NF-κB is its intracellular counterpart. Cytokines are effective in minute quantities and their functions are pleiotropic and redundant. Thus, therapeutic access to these messenger substances can occur only through low concentrations of active substances able to combine in many different ways, as exemplified by antihomotoxic combination preparations, whose working mechanisms are discussed in this article.

Introduction

Antihomotoxic medicine is generally considered a close relative of homeopathy. This view disregards the fact that antihomotoxic remedies, although produced according to official homeopathic guidelines, are symptom-specific in their application, while homeopathic remedies are not.[1,2] In homeopathy, each individual patient is treated according to a Principle of Similars discovered by comparing his or her symptoms to a remedy's so-called 'drug picture,' the list of symptoms induced by administering the remedy to other people (healthy test subjects, cured patients, cases of poisoning). Thus a homeopathic remedy's effect is patient-specific. "The same remedy that eliminates one patient's symptoms may be totally ineffective in another."[3]

Resumen

La medicina antihomotóxica se considera como un pariente cercano a la homeopatía. Este punto de vista desatiende el hecho que las preparaciones antihomotóxicas, aunque producidos según principios homeopáticos oficiales, son específicos a los síntomas, mientras que los remedios homeopáticos no lo son.[1,2] En la homeopatía, cada paciente se trata según un Principio de Semejantes que se descubre por una comparación de sus síntomas con los síntomas producidos por un remedio en pacientes sanos, pacientes curados, y casos de envenenamiento. Entonces, el efecto de un remedio homeopático es específico al paciente. "El mismo remedio que elimina los síntomas de una paciente puede ser totalmente ineficaz en un otro paciente."[3]

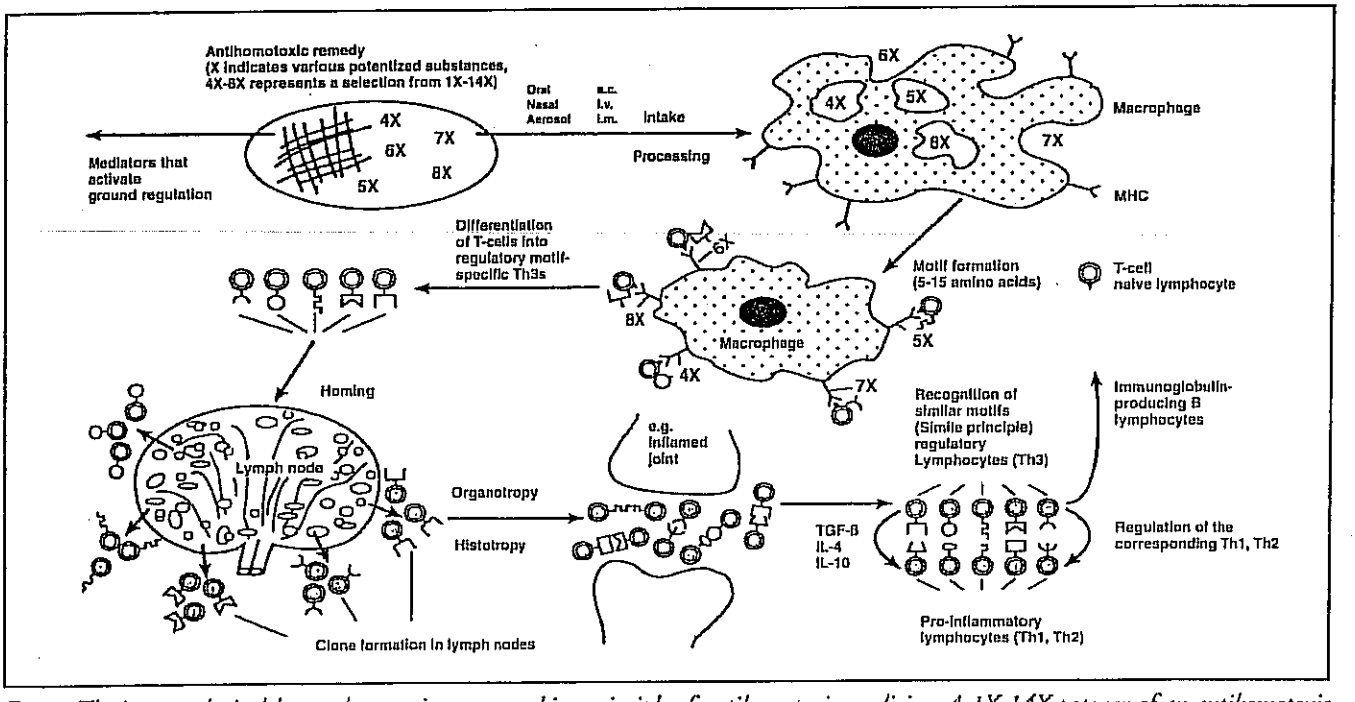

Fig. 1: The immunological bystander reaction as a working principle of antihomotoxic medicine. A 1X-14X potency of an antihomotoxic combination preparation contains enough of the active substance to stimulate macrophages/monocytes to produce motifs (upper row). Motif production is the prerequisite to the formation of regulatory lymphocytes (Th3–middle row). TH3 cells are chemotactically drawn to and downregulate proinflammatory lymphocytes (T4 and its subgroups Th1 and Th2).

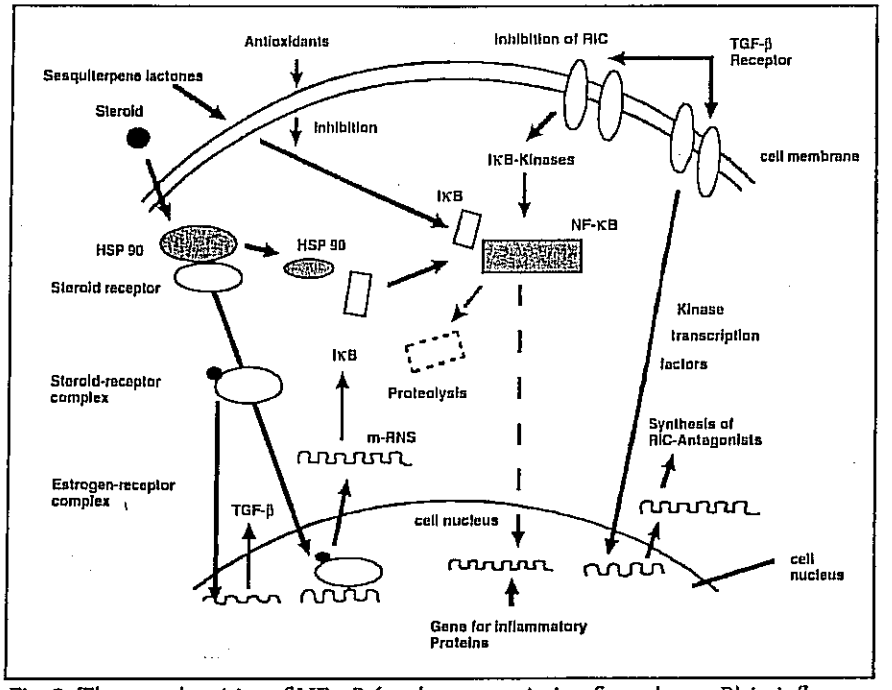

Fig. 2: The central position of NF-κB (nuclear transcription factor kappa B) in inflammation. The diagram depicts various ways of inhibiting NF-κB (broken arrow: inhibition of synthesis of inflammatory proteins; dotted rectangle: proteolytic breakdown of the IκB subunit that inhibits NF-κB. In addition, non-NF-κB mediated synthesis of TGF-β and of the receptor antagonists of inflammatory cytokines is also depicted. RIC = receptors of inflammatory cytokines, HSP90 = heat-shock protein 90.

Although antihomotoxic medicine makes use of homeopathic drug pictures in its search for appropriate treatments, each antihomotoxic remedy is specific only to the organ or tissue it targets; that is, its effect, like that of an allopathic drug, is not specific to an individual case. As is also the case with allopathic medications, we must be able to prove how antihomotoxics work. The purpose of this article is to supply such proof.

This paper on the working mechanisms of antihomotoxic medicine is based on studies published by the Institute for Antihomotoxic Medicine and Ground Regulation Research[1,4,5,6] and on relevant details from the international literature on the effects of minute doses of proteins. Overviews by Weiner and Mayer[7] and Garside and Mowat[8] served as background material.

The immunological bystander reaction in antihomotoxic medicine

As our own studies have shown, the potencies (primarily 2X through 8X) of organic proteins contained in potentized combination preparations (antihomotoxics) are especially suited to inducing the immunological bystander reaction. To the best of our knowledge, this reaction runs its course as follows (Figure 1): Regardless of how a potentized combination preparation is administered, its content of low and mid-range potencies of plant and animal proteins is absorbed by macrophages (or also by the related M cells of the intestinal mucosa) and digested via proteasomes. Small portions are returned to the cell's surface in the form of "motifs," chains of 5 to 15 amino acids, where they are linked to major histocompatibility complexes (MHC-I). When "naive" lymphocytes not marked with motifs of this type pass by, they transform themselves into regulatory Th3 lymphocytes by picking up motifs from the MHCs and binding them to their own receptors.[7,9,10] The Th3 lymphocytes migrate immediately into the nearest lymph node, where they multiply, forming a different clone of regulatory lymphocytes (Th3 cells; h stands for "helper") for each motif. It is important to note that the formation of Th3 cells is induced only by substances in the potency range indicated above (very low-dose antigen range), equivalent to about 1-10 µg per day per kg of body weight. More concentrated proteins inhibit Th3 cell formation, while potencies above 15X do not stimulate motif formation by macrophages.[1,5]

The marked Th3 cell clones move out of the lymph node and are carried throughout the body by the blood and lymph streams. When inflammation occurs, chemokines, complements, and other chemotactic factors draw the Th3 cells to the focus of inflammation, where they encounter pro-inflammatory T4 lymphocytes and their subpopulations of Th1 and Th2 cells. The motifs which pro-inflammatory lymphocytes carry on their surfaces include antigens from the focus of inflammation (such as collagen motifs from an arthritic joint). The presence of a similar motif on the surfaces of the regulatory lymphocytes (the Principle of Similars on the level of molecular biology) is enough to immediately trigger the release of transforming growth factor beta TGF-β. This cytokine downregulates the inflammatory leukocytes, and the IL-4 and IL-10 they release bolster the effect of TGF-β.[10] At this point it is significant to note that Reckeweg's multi-stage *auto sanguis* therapy boosts the immunological bystander reaction.[1,7,9-11]

The immunological bystander reaction offers a solid explanation for the well-known anti-inflammatory and analgesic effects of antihomotoxic therapy (as in rheumatic diseases, for example) reported by prospective studies.[1,4,5]

Cellular mechanisms in the inhibition of gene expressivity of proinflammatory cytokines

The cellular response of pro-inflammatory cytokines (IL-1, IL-2, IL-3, Il-6, Il-8, TNF-α) is linked to activation of nuclear transcription factor kappa B (NF-κB).[12-15] (Figure 2). NF-κB is present in the cytoplasm in an inactive form, linked to the inhibiting subunit IκB.[12,15] IκB kinases, which break down IκB and activate NF-κB through phosphorylation, are activated

when proinflammatory cytokines bind to receptors on the cell membranes[12-15] (Figure 2).

NF-κB also controls transcription of the genes for immune receptors, cell adhesion molecules, hematopoietic growth factors, growth factor receptors, and cyclooxygenase II (see [15] for an overview). In addition, NF-κB controls various genes necessary for the formation of proteins needed for presenting antigens on the cell surface. These proteins include MHC-I molecules, β2 microglobulin, TAP1 transporter (which transports peptides into the cell's endoplasmic reticulum) and the proteasome subunit LMP2, which is important in peptide synthesis.[12, 15]

Thus NF-κB plays a central role in general inflammatory and immune processes.[1,15, 16] Over-activation of NF-κB is present wherever inflammation occurs.

Reduction of over-activation of nuclear transcription factor Kappa B (NF-κB)

The TGF-β released by TH3 lymphocytes in the course of the immunological bystander reaction induces an anti-inflammatory response. We know enough about the cellular mechanisms involved to say that after TGF-β binds to its cellular receptors, IL-1 receptor expression is inhibited while the synthesis of IL-1 receptor antagonists is induced. It seems that the synthesis of other pro-inflammatory cytokines is also inhibited.[17] (Figure 2).

Regulation of NF-κB by antioxidants

Free oxygen radicals, which develop normally in the cell in the process of mitochondrial respiration, are reduced by the cell's endogenous oxidation-reduction systems and ultimately transformed into water. NF-κB is activated by excess oxygen radicals and inhibited by endogenous antioxidants such as n-acetylcysteine or α-lipoic acid, which are present in all plant and animal cells and are therefore also components of the low to mid-potency portion (1X-14X) of antihomotoxic combination preparations.

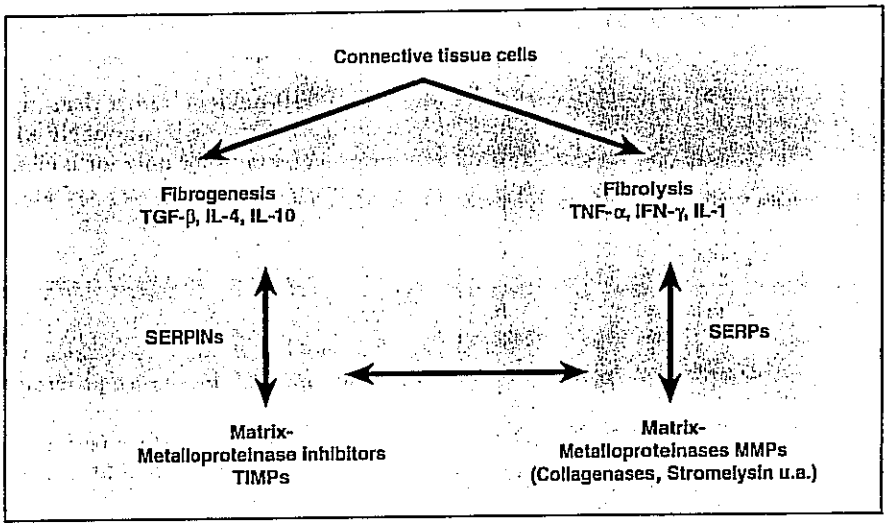

Fig. 3: Control of feedback between fibrogenesis and fibrolysis by an anti-inflammatory, fibrogenic cytokine contingent (TGF-β, Il-4, IL-10) and a pro-inflammatory, fibrolytic cytokine contingent (TNF-α, IFN-γ, IL-1); TGF-β = transforming growth factor beta; IL = interleukin; IFN-γ = interferon gamma; TNF-α = tumor necrosis factor alpha; SERPs/SERPINs = serine proteases/serine protease inhibitors (e.g. plasmin/antiplasmin); TIMPs = tissue inhibitors of metalloproteinases.

Regulation of NF-κB by sesquiterpene lactones

Of the approximately 30,000 naturally occurring substances whose structures were known at the time of Fischer's 1991 overview, 3,000 were classed as sesquiterpene lactones.[18,19] Sesquiterpene lactones are found primarily in the species-rich Asteraceae family. For antihomotoxic medicine, one of the most important substances from these species is arnica, whose anti-inflammatory effects have long been known. Studies show that arnica's sesquiterpene lactones, particularly helenalin, selectively inhibit NF-κB over other transcription factors (OCT-1, S1, STAT-5).[15] In cell cultures, helenalin has the strongest anti-inflammatory effect when it is present in the lower MM range.[15] Presumably, helenalin prevents activation of NF-κB by causing covalent interlocking of its p50 and p65 protein subunits.[15] (Figure 2).

Extrapolation from the arnica content of anti-inflammatory antihomotoxic preparations such as Traumeel® and Zeel® indicates that their sesquiterpene lactone contents are lower by a factor of 1,000 (that is, in the nanomol range), which means that they still have direct anti-inflammatory effects but fall into a toxicologically safer range. (As might be expected, therefore, these antihomotoxic preparations have no known arnica-related side effects.)

Regulation of NF-κB by plant and animal steroid hormones

Steroids can inhibit inflammatory processes. In the case of corticoids, we must distinguish between effects that are independent of the cell nucleus (i.e., not genome-mediated), such as those of hydrocortisone, and specific receptor-dependent, genome-mediated effects of glucocorticoids.[20]

The effects of hydrocortisone, which are bound to the cell membrane, develop because the substance binds to the lipocortin-1 receptor on leukocytes, thus arresting activation and further production of pro-inflammatory cytokines (see [20] for an overview). It is not known whether this process occurs directly, by inhibiting NF-κB, or indirectly, by subsequently activating the inhibitory subunit IκB, as in the case of cytoplasmic steroid hormone receptors.

After passively diffusing through the cell membrane, glucocorticoids, like mineral corticoids, bind to cytoplasmic steroid receptors (Figure 2; see [20] for an overview), triggering a conformation change in the receptor that causes the release of the heat-

Component	Cytokine
Aconitum napellus	TGF-β
Arnica montana	TGF-β
Atropa belladona	TGF-β
Bryonia cretica	TGF-β
Chamomilla recutita	TGF-β
Conium maculatum	TGF-β
Echinacea angustifolia	TGF-β
Euphorbium	TGF-β
Funiculus umbilicalis suis	TGF-β
Placenta suis	TGF-β
Rhus toxicodendron	TGF-β
Sanguinaria canadensis	TGF-β
Sinusitis-Nosode	TGF-β
Hepar sulfuris	TNF-α
	TGF-β
	IL-10
	IFN-γ
Pulsatilla	TNF-α
	TGF-β
	IL-10
	IFN-γ

Table: Selection of potentized (2X-6X) extracts of plants or animal organs tested on TGF-β synthesis by leukocytes in whole-blood cultures (see [27] for methodology). Hepar sulfuris and Pulsatilla were also tested for their effects on other cytokines, some of which promote inflammation.

shock protein (HSP 90) associated with the receptor.[13, 14, 20] The heat-shock proteins belong to a family of proteins produced by cells in response to various influences.[21] Thus activated, the steroid receptor complex can then bind with cytokine-activated transcription factors such as NF-κB in the nucleus and directly prevent their activation.[14,20] In addition, steroid receptor complexes in the nucleus can increase transcription of the IκB gene. The resulting increase in IκB synthesis continues to inhibit NF-κB.[12,14] (Figure 2).

Regulation of TGF-β by the estrogen receptor

The genes responsible for transcription (and thus also for the synthesis) of TGF-β are subject to control by the estrogen receptor that develops on all connective tissue cells.[22] (Figure 2). This relationship to the estrogen receptor is important for understanding bone metabolism and estrogen treatment for osteoporosis; it also explains the use of Ovarium compositum in antihomotoxic therapy for osteoporosis.

The TGF-β receptor, rather than triggering TGF-β synthesis by way of NF-κB, seems to be responsible only for inhibiting synthesis of inflammatory cytokines and for its own production.[14, 17, 22, 23]

Discussion

The cytokine network in an organism functions on the principles of pleiotropy (a single cytokine has several different effects) and redundancy (different cytokines have the same effect). (See [24] for an overview). For example, TGF-β is pleiotropic with regard to connective tissue build-up, while interleukins 1, 2, 4, 7, 9, and 12 are redundant because all of them are capable of stimulating division in activated T lymphocytes.[24]

Antihomotoxic combination preparations reflect cytokine activity of this sort and permit the organism to select the ingredients that match its condition. The concentration of substances in antihomotoxic combination preparations frequently falls into the nanogram range, the range in which maximum cytokine activity also develops.[25]

The cytoplasmic nuclear transcription factor NF-κB plays a central role in the transmission of information from pro-inflammatory cytokines to the cell's genetic material. NF-κB transmits incoming information to the gene segments responsible for pro-inflammatory cytokine synthesis.[12, 14, 15, 26]

On the basis of the immunological bystander reaction, TGF-β functions as a switch in the cytokine-controlled balance between fibrogenesis and fibrolysis (Figure 3). TGF-β, supported by interleukin 4 and interleukin 10, always stimulates inhibitors of proteolytic enzymes, which can also release TGF-β from the latent form bound to matrix substances. Proteolytic breakdown of tissue releases this tissue-bound supply of TGF-β, which can then intervene in the regulation of inflammation.[1, 5, 23]

Antihomotoxic combination preparations contain proteins that can stimulate immune-competent cells, granulocytes, and fibroblasts to synthesize both fibrogenic and fibrolytic cytokines.[1] Depending on the situation, the synthesis of either anti-inflammatory or pro-inflammatory cytokines may predominate. For example, in an inflammation involving raised levels of IL-1 and TNF-α, among others, the immunological bystander reaction makes more TGF-β available to downregulate the process. In the opposite instance, when excessive tissue formation occurs as a result of too much TGF-β, TGF-β is reduced by making more IL-1 and TNF-α available.[5, 27]

Evidently, each tissue or organ has a characteristic inflammatory infiltrate with a specific combination of chemotactic cytokines (chemokines). (See [28] for overview.) These constellations of chemokines influence the homeopathic drug picture that corresponds to an illness. Thus we can understand why different illnesses require different single remedies or combinations of remedies. For example, antihomotoxic suis organ preparations help regulatory lymphocytes find their way to the right tissue or organ. The suis organ preparations contain potentized proteins related to a particular tissue or organ. These proteins are bound to the surface of leukocytes or broken into the motifs used in differentiating T cells into regulatory Th3 lymphocytes. Organ-specific combinations of chemokines then draw these cells directly to where they are needed .

This connection between the homeopathic drug picture and cytokine-controlled immunomodulation suggests that antihomotoxic medicine, while it clearly bridges the gap between classical homeopathy and academic medicine, is a distinct and autonomous discipline.

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