PHARMACOLOGICAL ASPECTS OF GISENG. A REVIEW.

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It is probably not a secret that potential pharmacological or therapeutic activities of ginseng are widely unknown among physicians in the Western world or that the medicinal use of ginseng is even in disrepute in these countries. If one consults German or Anglo-American standard textbooks of pharmacology and therapeutics one will find that in most of them ginseng is even not mentioned (39, 24, 27). One or the other of such books may contain a short notice about ginseng, but usually without exact data on pharmacological actions (66). About the same is true regarding publications in pharmacological journals of the Western hemisphere. In the last decade only very few papers dealing with pharmacological or clinical studies on ginseng have been published in the above mentioned journals.

Somewhat more work has been devoted to pharmaceutical or chemical problems, i.e. to the composition of ginseng. Several constituents have been isolated and described as to their chemical and physi cal properties (28, 29, 30, 33, 69).

The above mentioned situation regarding the presentation of ginseng in pharmacological textbooks is paralleled by the fact that in official pharmacopeias and drug registers no or only a few ginseng containing drugs are listed. It was impossible to find in the competent German books a drug consisting of ginseng as the sole component. There are, however, a few drugs on the market which contain ginseng extract as one among other constituents. These are drugs which are prescribed by physicians as tonics or geriatrics.

On the other hand, ginseng possesses among the population a certain popularity also in Western countries. This may be illustrated by the following a story which was reported in a German newspaper to have happened in September 1974 in Berlin. A man entered a herb shop, threatened the owner with a gun and demanded two parcels with ginseng roots. This story also shows that there exists a market for ginseng at a—as one might call it—'submedical level'. Ginseng extract and ginseng containing preparations, such as ginseng vine, ginseng tea, ginseng dragees etc., are offered at so called reform houses, ware houses, groceries and similar shops, i.e. outside of any legal, medical or pharmaceutical control. This situation has caused criticism for several reasons. One reason is due to the fact that some of these ginseng preparations have been introduced by unserious publicity campaigns. Another reason was and is the fact that ginseng preparations may contain pharmacological quite active constituents about which not enough is known; this concerns the activities themselves as well as the does-response relationships. Furthermore it was criticized that the qualitative and quantitative composition of ginseng extract can vary due to the origin of the used ginseng roots and the extraction procedures applied. It was

also quoted that the free sale of such ginseng preparations is in contradiction with drug legislation.

It appears desirable, therefore, to obtain exact knowledge on the pharmacological properties of gi nseng, in order to find out if any or which of the pharmacological activities could be utilized the rapeutically, particularly also with regard to present drug laws, and in order to see, whether or not any dangers may be connected with the free sale of ginseng. I have tried, therefore, to summarize the present state of knowledge regarding the pharmacology of ginseng with particular consideration of results obtained during the last decade. During this time quite a lot of experimental work has been performed in Korea and Japan, but also in China, Russia and Bulgaria, and a rather broad spectrum of different pharmacological activities of ginseng has been reported. With regard to the pharmacological active principles of ginseng one must distinguish investigations which have been done with the total extract from such investigations in which more or less purified fractions of the extract or chemically exactly defined individual constituents from ginseng were used. The situation is further complicated by the fact that not only extracts from ginseng roots, but also extracts from other parts of the plant, such as leaves or callus, have been applied. Furthermore the composition of the total extract or individual fractions may vary due to the species of ginseng, the place of origin, methods of growth or culture, technique of extraction and various other factors. Most pharmacological investigations in the past have been performed with total extracts from ginseng roots. In review articles on the pharmacological or biological activity of such extracts which have been published one or two decades ago we usually find the following types of activity mentioned (56, 60, 63):

1. Ginseng extracts are said to increase the capacity for physical work and intellectual performance.

2. Ginseng preparations administered during prolonged periods are reported to accelerate recovery from diseases. In this connection it is sometimes emphasized that ginseng preparations do not show any unwanted side effects and that they do not lead to tolerance.

3. Quite frequently gonadotropic actions of ginseng have been described.

4. A completely different type of action is the anti-inflammatory effect which is attributed to ginseng.

5. Particularly in the lay press a so called 'adaptogenic effect' has aroused much interest. This adaptogenic action refers to an increase of the reactivity in stress situations and an increase of the defensive forces of the organism.

6. Influences of ginseng on metabolic functions, particularly on the carbohydrate metablism, have been discussed.

7. Not easy to interprete are ginseng effects on the central nervous system: In these early papers tonicising and stimulating as well as depressing effects on the central nervous system were described.

Some of the activities mentioned above are pharmacologically not very well definable and may involve simultaneously several organs or functions of the body or may enclose various types of pharmacological actions. In part the findings reported even seem to be contradictory. It therefore appears necessary to try to analyse the whole complex of ginseng activities regarding effects on single organs, tissues and cells or on single functions. Such an analysis would be facilitated if it could be based on investigations with chemically exactly defined individual constituents of the plant. A few pharmacological investigations with isolated constituents from ginseng, such as β-sitosterol, oleanic acid or panaxadiol were performed already 10 to 15 years ago and during the last years work with purified fractions or isolated constituents has increased, but even at the time being the majority of published investigations seems to have been executed with the total extract. With regard to the large number of quite different chemical compounds which have been detected in ginseng until now opposite actions or contradictory results are probably not surprising.

A number of investigations performed during the last years aim at demonstrating effects of ginseng preparations on adaptation, resistance and capacity for work under standardized conditions. It could be shown, for example, that ginseng extracts increases the duration of running ability (65) or prolonged si-

:gnificantly the swimming time of rats (67). Further investigations (4) revealed that glycoside constituents from ginseng may be responsible for the stimulating effect on running performance of animals. A number of sterolglycosides and genins isolated from ginseng were from 10 to 100 times more effective than the crude extract itself.

It is of interest that some ginseng activities are only demonstrable in stressed, impaired or injured animals. Therefore various types of experiments were designed using animals submitted to biological, physical or chemical damages. It could be shown that pretreatment with ginseng extracts attenuated experimental trypanosomiasis in mice and prolonged their survival time (48);

in rabbits ginseng prevented the development of fever induced by typhoid or partaypohoid vaccine. -Liver damages caused by carbon tetrachloride or irradiation were partially prevented by the administration of ginseng extract (13). The resistance of frogs against the toxic effects of high doses of the heart glycoside gitalin was increased by pretreatment with ginseng (57). Not quite clear are interactions between ethanol and ginseng extract. Antagonistic as well as synergistic actions of ginseng with the depressing effects of ethanol on the central nervous system have been described (69, 3).

A number of investigations deal with protective effects of ginseng against cold or heat exposure. Here again usually no influence of ginseng on normal animals kept at room temperature was demonstrable (48, 3). Ginseng extract, however, was capable of preventing changes of the body temperature in animals exposed to cold or heat under various experimental conditions (12, 17). Another parameter used to indicate protective ginseng effects in temperature stressed animlas is the adrenal ascorbic acid (11). In animals under normal temperature conditions ginseng was without any effect on the adrenal ascorbic acid content. After exposure to cold or heat, however, ginseng caused at first a faster decrease and subsequently a fast normalisation of the adrenal ascorbic acid content, while in untreated control animals a further decrease of the values occurred (10, 18). These results indicate that ginseng facilitates the reaction to and accelerates the recovery from temperature stress. Further types of physical stress applied are the immobilization of animals and the exposure to positive radial acceleration or to low pressure respectively. In immobilized animals collapse occurs after a certain time. The interval until the occurence of collapse was prolonged by ginseng extracts as well as by a number of isolated ginseng glycosides. Changes in the weight of body organs and of some biochemical parameters which are usually connected with this type of stress were also prevented by the treatment with ginseng glycosides (5). The survival of rats exposed to low presure (190 mm Hg) was enhanced after the treatment with ginseng (64). Likewise the tolerance of mice against the stress of positive radial acceleration was increased by the application of ginseng (16, 19). A number of blood parameters, such as serum protein content, hemoglobin level, hematocrit and red blood cell count, which are depressed by exposure to this type of stress were also normalised by the treatment with ginseng.

Similar antistress effects as were observed with ginseng preparations could in some cases also be demonstrated by treatment of stressed animals with the adrenocortical hormones cortisol or cortisone.

This leads us to potential effects of ginseng preparations on the endocrine system or to hormone like actions of ginseng itself. The question has been put forward whether particularly the antistress activities of ginseng but also other actions of ginseng preparations are mediated via the adrenal cortex or the adrenocortico-pituitary system. At the time being this question is probably not definitely to be answered. Some findings seem to point at an involvement of this system, others do not. It could be shown for example, that ginseng extracts exert a stimulating action on glucocorticoid production (54), and that they prevent stress induced weight changes of the adrenals and stress induced changes in the adrenal ascorbic acid and cholesterol content (10, 18, 5, 38). Adrenalectomized rats lost their ability to withstand temperature stress which they have under the influence of ginseng (64), while in other experiments ginseng preparations exerted antistress activities also in adrenalectomized mice (17). Other effects of ginseng preparations, such as a stimulation of serum

protein synthesis (47) or the prevention of a decrease of ATP, glycogen or creatin phosphate caused by exercise (7) could not be shown to be mediated through the adrenal glands.

Another organ of the endocrine system which was considered to be responsible for ginseng activities in the organism is the thyroid gland. Investigations designed to clear the role of the thyroid led, however, to contradictory results: Inhibitory as well as stimulating effects of ginseng preparations on thyroid function were observed (55, 62).

Less doubtful are sex hormone like activities of ginseng preparations. The great popularity of ginseng is based probably to a large degree on constituents with this character. Some recent investigations have furnished further evidence for the occurence of sex hormone like compounds in ginseng. In experiments using mesenteric mast cells as indicator ginseng preparations showed the ability to decrease deteriorating effects due to a lack of testosterone resulting from castration (36). Gonadotropic effects could be shown to be exerted by sterolglycosides isolated from ginseng (4), and by thin layer chromatography estrone, estradiol and estriol were detected in the liposoluble fraction of ginseng extracts (1). The occurence of constituents with sex hormone activity in ginseng preparations thus seems to be proven. But as ginseng extracts probably can contain compounds with male as well as female sex hormone character questions concerning concentrations of individual compounds and ratios between male and female hormones remain to be solved. With ginseng effects on the endocrine system or with hormone like actions of ginseng influences on metabolic processes may be connected, and during the last years a lot of work has been devoted to this topic, particularly to potential effects on energy and carbohydrate metabolism. But in this field too, many questions still remain to be answered. In older publications antihyperglycemic effects of ginseng have been reported (6).

In later investigations, however, also increases of blood glucose due to administration of ginseng or glycosides from ginseng were observed(8, 9). This increase of blood sugar was accompanied by an increase of liver and muscle glycogen and a decrease of inorganic phosphates in blood. Other investigations seem to indicate that ginseng extract causes a more economical release of body energy (61), and a more economical use of glycogen and high energy phosphates during exercise; the energy supply for muscle activities seems to be improved (23). The ginseng constituent panaxoside S could be shown to exert similar effects as the total extract; it prevented the decrease of ATP, glycogen or creatin phosphate which goes along with forced exercise (22). The cellular or molecular mechanism of these actions is not clear. It was suggested that ginseng extract may influence the enzyme systems involved in gluconeogenesis and glucogenesis (73).

The just mentioned effects on energy metabolism may play a part in ginseng effects on nutrition and body weight or on enhanced recovery from diseases respectively. There is some experimental evidence for such activities. Ginseng preparations prevented the decrease of body weight in a carbohydrate deficient group of rats, were however without any effect on rats under normal conditions (73). Other investigations have shown that ginseng extract enhances eating frequency and body weight in normal rats and prolongs survival time of food deprived rats (34). In humans living under somewhat extreme conditions a reduction of basal metabolism was caused by ginseng preparations (22).

No effect of ginseng on the oxygen consumption of mice kidney and liver in vitro was detectable (60), while the respiration of isolated rat cerebral cortex slices was decreased by ginseng saponins; on the other hand ginseng saponin increased respiration of cortex slices which had been depressed by previous treatment with amphetamine (21). At present no definite conclusion can be drawn, whether the above mentioned effects on metabolism are due to a local effect of ginseng at the cellular level or whether these effects are mediated through the endocrine or nervous system.

Another kind of a potential metabolic activity of ginseng preparations concerns the lipid metabolism. Early investigations with sitosterol isolated from ginseng (33) did not furnish clear results regarding influences on serum cholesterol level. In recent investigations, however, prolonged treat-

ment of rats with ginseng saponins led to a decrease of total serum cholesterol, while serum phospholipids initially increased and subsequently significantly decreased (50).

Potential effects of ginseng extracts on the central nervous system are another important topic to be discussed. In older publications stimulating as well as depressing effects on the central nervous system were described. And similar, ambiguous seeming results were also obtained in more recent studies. Thus ginseng extracts have been shown to reduce sleep frequency and to increase walking behaviour (34), while other investigators report a decreased spontaneous activity of rats (43, 64). Ginseng extract were found to prolong the central depressive effects of barbiturates and ethanol (69), while in other studies an antagonistic effect against the depressing action of ethanol was observed (3). Ginseng extract could be shown to activate the EEG of normal rabbits and to diminish the inhibitory effects of sedatives such as chloral hydrate and medinal (41, 42, 61). This confused appearing situation can probably only be elucidated through investigations using separate purified fractions of the extract or if available isolated and chemically exactly defined individual constituents. A few studies directed at this aim have recently been published. A mixture of neutral ginseng saponins could be shown to exert central nervous depressive, ataractic, analgesic and central myorelaxant effects, while a mixture of certain ginseng steroids was found to possess central nervous stimulant as well as depressent activity (68).

A similar situation as with the central nervous system exists regarding potential ginseng effects on the vegetative nervous system and on vegetative innervated organs. Ginseng extracts were reported to increase or to decrease blood pressure, to stimulate or to inhibit intestinal movements, to inhibit and to stimulate respiration, to have or not to have an antihistaminic action (52, 53, 31, 48, 70, 58).

Here, too, elucidation is probably only to be expected by a detailed study of isolated and chemically defined constituents from ginseng. Already a few years ago it could be shown that certain fractions from ginseng caused an increase of blood pressure, while other fractions exerted the opposite effect; some fractions inhibited respiration, the total extract agitated respiration (31). In other studies fractions with papaverin like activities (this would mean a spasmolytic effect) and other fractions with muscarinic and histamine like substances were discovered (68).

By some authors influneces of ginseng extract on the blood system were described, such as an increase of erythropoietin level (49) or an increase of the red blood cell count, the hemoglobin content and the hematocrit (15, 16, 20). On the other hand a part of a number of tested ginseng saponin fractions exhibited potent hemolytic activities in vitro. Other saponin fractions, however, inhibited hemolysis induced by lecithin or deoxycholate (44).

In former publications ginseng extracts were reported to possess antiphlogistic properties. There are only a few newer studies demonstrating such activities. It could be shown that ginseng extract reduces capillary permeability which had been increased by the application of irritative substances and that this action is comparable to that of some non-steroidal antiphlogistic drugs (26). It is doubtful whether the anti-inflammatory action of ginseng is brought about by a stimulation of the adrenal cortex (54), as ginseng extracts were found to exert antiinflammatory activities also in adrenalectomized animals (25).

Some recent studies have been devoted to the question of potential effects of ginseng extracts on cell viability, cell growth and cell multiplication. Ginseng extracts could be shown to inhibit growth of certain experimental tumors, such as sarcoma 180 and adenocarcinoma 755, while an experimental leukemia in mice was not influenced by ginseng. The oncolytic actions of ginseng were accompanied however by toxic side effects (40).

Experiments designed to test ginseng influences on the inoculability of intravenously introduced tumor cells did not show clear results (71). On the other hand, protective ginseng activities for cells could be demonstrated: Ginseng extract delayed the degeneration and prolonged the post-mitotic life span of human amnion cells cultured in vitro (74). These results again seem to indicate that ginseng may contain constituents with opposite activities, namely

with cytostatic as well as with cell protective or cell stimulating properties. Some evidence for this assumption may be deduced from the finding that lignans isolated from ginseng leaves inhibited protein biosynthesis of cultured cells, while this inhibitory effect was reduced by flavonoids (2). Influences of ginseng extract on protein synthesis were also demonstrated with other experimental models. Thus it was shown that certain fractions from ginseng root extract increase serum protein synthesis (47).

Finally I would like to mention some recent studies concerning ginseng influences on nucleic acid synthesis or on the nucleic acid content of certain organs respectively. In some of these investigations no influences of ginseng on nucleic acids were detectable, in other experiments either an increase or a decrease of nucleic acid synthesis or content was found. A stimulating effect could be observed particularly in animals with a stress induced depression of nucleic acid synthesis or content (14, 51, 37., 35, 72). Furthermore individual organs may show different responses. Thus ginseng increased the DNA and RNA content in the adrenals, depressed the content of both nucleic acids in the liver and pancreas, while in the spleen RNA was enhanced and DNA reduced (51). In contradiction to some of these results are findings of other authors who observed an increase of RNA content or synthesis in liver (46, 32, 45).

This short survey shows that ginseng contains constituents which are able to exert many quite different pharmacological actions. This may explain the fact that in studies using the total extract variable and sometimes contradictory results were obtained. Despite the fact that particularly in the last years much work has been performed in order to elucidate the pharmacology of ginseng many problems still remain to be solved. From my personal view as a pharmacologist I would suggest that particularly more pharmacological studies with individual, chemically exactly defined constituents from ginseng are necessary, in order to get a clear picture of the pharmacological properties of ginseng, and in order to see which of the constituents may possess comparable or better or perhaps other pharmacological actions than drugs known hitherto.

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