GINSENG, CORTICOSTEROIDS AND THE RESPONSE TO STRESS

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Panax ginseng is widely used in traditional oriental medicine as a restorative, tonic and prophylactic agent. It is claimed to be able to increase vitality and resistance to stress and disease[1]. However the concept of a pharmacological agent that increases general resistance is novel to Western medicine and it would be of great interest to be able to securely demonstrate that it does indeed have such a pharmacological activity and determine the mechanism and site of its action. My research is directed towards this end.

The first indication that there is a mechanism for general stress resistance was provided by Hans Selye in his classic work on the physiological processes of adaptation. He showed that the stress reaction is controlled by the adrenal glands through the production of steroid hormones. Prolonged stress could eventually exhaust the body's resistance. Exhaustion is characterised by hypertrophy of adrenals, depletion of precusors for steroid synthesis and damage to a number of body systems through excessive steroid secretion.

Using this experimental model Professor I. I. Brekhman found that ginseng and some other oriental medicinal plants were capable of increasing the resistance of experimental animals to a wide variety of stresses whether physical, chemical or biological[2]. This suggested that ginseng somehow increased the capacity of the adrenal glands to cope with stress. Further work confirmed this using both ginseng and its constituent terpenoidal glycosides. Ginseng was found to prevent depletion of the adrenal ascorbic acid during stress[3] and to reduce other indices such as adrenal hypertrophy, and eosinophil levels[4].

Removal of the adrenals abolishes many of the effects of ginseng. An interesting series of experiments by C. Kim and colleagues supported the supposition that ginseng acts directly on the adrenal glands. He injected adrenocorticotropic hormone (ACTH) into rats and demonstrated that ginseng treated animals responded more quickly to the ACTH but that the adrenal capacity was subsequently more rapidly restored[5]. Yet there are other studies which throw doubt on the adrenals as a site of action. For example I have shown that ginseng causes human cells in culture to divide more rapidly and alters their growth properties in a manner exactly analogous to hydrocortisone[6].

The situation is made more complex and confusing because of the wide variety of physiological and metabolic changes reported in ginseng treated animals[7], which are rarely discussed in terms of steroid action. It was therefore felt that it would be appropriate to test the effect of ginseng on steroid action in the absence of the adrenal glands. Also since the brain is in ultimate control of both the stress mechanism and the level of fatigue or activity,

the best system to use would be the examination of the interaction of steroids on the brain.

The main experiment set out to test if ginseng affected the binding of corticosteroids to the brain of rats. It was carried out by Deepak Kumar Shori of the Department of Pharmacology, Chelsea College, Manresa Road, London. Female rats were adrenalectomised and ovariectomised when they had reached approximately 160 gm weight. They were then given 5 mg /day of crude aqueous ginseng extract or 0.5 mg/ day of a more purified saponin mixture, supplied by the Research Institute of the Office of Monopoly in Seoul. The ginseng was given as an intraperitoneal injection for seven days. Control mice received saline. Four hours after the last injection tritiated corticosterone was administered (. 083 milliCurie per rat). The rats were sacrificed, the brain removed and dissected. Different sectors of the brain were homogenised and fractionated.

The amount of radioactivity in the nuclear fraction was measured. This represents binding of corticosterone to the brain. The results are given in the following table. Each experiment represents the pooled data of three ginseng treated and three control rats making 36 rats in all.

Table Amount of corticosterone bound to nuclei in different brain regions (femtomoles per mg. DNA)

	Expt.	Cortex	Septum	Hippocampus	Hypothalamus	Amygdala	Pituitary
Control	1.	0.4	2.0	1.6	1.3	0.0	0.5
	2.	2.8	7.4	29.6	2.2	7.5	2.2
	3.	1.2	2.0	1.1	0.9	0.6	0.2
	4.	2.5	6.3	47.4	5.4	6.8	1.3
	5.	1.9	5.1	51.6	0.4	3.6	0.4
	6.	5.7	12.3	70.3	1.2	10.3	1.6
	Mean	2.42	5.85	33.6	1.9	4.8	1.03
Ginseng	1.	4.0	15.0	99.0	0.6	23.2	2.1
	2.	10.4	25.5	121.6	2.7	25.4	2.8
	3.	14.2	98.1	120.8	7.8	27.0	9.1
	4.	10.5	13.9	104.3	3.9	21.8	6.5
	5.	9.4	30.9	110.2	1.9	24.4	3.8
	6.	14.2	21.5	192.6	2.0	42.1	4.6
	Mean	10.4	34.1	124.8	3.2	27.3	7.97

The results show a major increase in the uptake of the steroid, especially in the hippocampus, amygdala and pituitary. In individual experiments the increases in ginseng treated animals varied from about two-fold to about a hundred-fold. The experiments were repeated with dexamethasone, a glucocorticoid analogue. No differences were found in uptake in different brain regions with this analogue, nor was there any difference in ginseng treated and control rats. We also measured the amount of corticosteroid in the serum two hours after injection and it was roughly three times higher in the ginseng treated compared to the control rats.

The findings reported here may explain some of the observations on stress resistance made by other workers. If ginseng treatment increases the uptake of glucocorticoid and the level of the steroid in the blood, this would account for the increased response to stress and the increased general resistance of stressed animals. At the same time since less steroid would be needed to achieve a given physiological effect it would explain why ginseng treated animals do not become depleted when subject to prolonged or severe stress. The raised eosinophil levels vanished ascorbic acid and adrenal hypertrophy in stressed animals, equivalent to the exhaustion phase discussed by Selye would indeed be delayed in ginseng treated animals if ginseng has a "steroid sparing" effect. It is also clear that the effect we observe has nothing to do with the adrenal glands as such since the animals are adrenalectomised. Therefore it is not correct to assert that ginseng acts solely on the adrenal glands.

There are basically three ways to interpret these results in terms of the site of action of ginseng. On the one hand the ginseng treated animals may remove corticosteroids from their blood more slowly so that there is a higher level in the body. Alternatively there may be more receptors in the neurones of ginseng treated animals to take up more steroid and pass it on to the nuclei. Thirdly, there may be an interference with the feedback of steroid levels in the body which is established by the hypothalamus, through the pituitary. Bearing in mind published work on the pharmacological effects of ginseng, I would favour the latter interpretation. However more work is needed to elaborate the mechanism and this is in progress. The fact that ginseng treated animals bind more steroid may help us to understand the well known antifati-

gue properties of ginseng[8,9]. For although we do not know exactly why the steroids bind to neurones in these different areas, it has been reported that they generate arousal and alertness. Fatigue is anyway a form of stress. Therefore an increase in steroid uptake could also lead to resistance to fatigue.

These results are potentially useful as a model with which to assay ginseng. The mouse swimming test is commonly used for this purpose, however it has distinct disadvantages because it is a behavioral rather than pharmacological model. A steroid binding test would be simpler and more reliable. These results are preliminary and further work is needed to eliminate artefacts. Nevertheless this may be the first clear demonstration of a biochemical change in the brain which is produced by ginseng.

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