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Suppression of Cellular Immunity by Surgical Stress and Effect of PSK

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Suppression of cellular immunity is one of the biological responses of hosts exposed to surgical stress. Surgical stress causes secretion of adrenal corticosteroids, as well as the production of cytokines and acute phase reactants. These factors are involved in the complex mechanism by which cellular immunosuppression is induced. The mechanism of cellular immunosuppression and the effect of preoperative treatment with protein-bound polysaccharide Kureha (PSK), a biological response modifier (BRM) were investigated in an animal model. In this model, cortisol and immunosuppressive acidic protein (IAP) levels were increased by surgical stress, resulting in the suppression of cellular immunity. The immunosuppressive effects of cortisol and IAP appeared to play an important role in the mechanism of immunosuppression due to surgical stress. In an attempt to minimize such immunosuppression, we treated rats with PSK preoperatively. PSK therapy was effective in suppressing the oversecretion of cortisol and the overproduction of IAP, and thereby prevent the postoperative impairment of cellular immunity. When malignant tumors are treated surgically, the cellular immunosuppression caused by surgical stress may assist the residual cancer cells to grow and metastasize. In this context, preoperative treatment with PSK may be useful to minimize such immunosuppression.

Introduction

Suppression of cellular immunity secondary to reduced immunocompetent cell function is one of the biological responses of hosts exposed to surgical stress[1)~6)]. Surgical stress causes secretion of various hormones (particularly adrenal corticosteroids), as well as the production of cytokines and acute phase reactants. Because a close interaction between the nervous, endocrine, and immune systems has been documented[7)], these factors are involved in the complex mechanism by which cellular immunosuppression is induced.

In cancer patients, this immunosuppression is an adverse reaction which enhances the postoperative growth and metastasis of cancer cells[8)~11)]. Therefore, it is desirable to minimize immunosuppression by surgical stress when cancer patients undergo surgery.

Accordingly, various biological response modifiers (BRMs) have been administered in attempts to minimize such immunosuppression[12)~17)], but their efficacy remains unclear.

The present study was designed to clarify the preventive effect of the BRM known as protein-bound polysaccharide Kureha (PSK) on suppression of cellular immunity due to surgical stress, particularly in terms of the changes of hormones, acute phase reactants, and immunocyte function.

Materials and Methods

1. Animals and tumor

In experiment I and II, male WKAH rats (7 weeks of age, Japan SLC, Japan) were used. To produce a tumor-bearing animal model, 1×10^6 KDH-8 tumor cells were inoculated into the right hind limb of each rat. All animal experiments were conducted in accordance with guidelines of Animal Care and Use Committee of Kureha Chemical Industry and Animal Experiment Ethical Review Committee of Tokyo Women's Medical University.

2. Experiment I

1) PSK administration and surgical treatment

PSK was dissolved in 0.9% NaCl for administration. After inoculation of tumor cells, 24 animals were divided into two groups; 12 rats received oral PSK (1,000 mg/kg daily) for 5 days (PSK group) and the other 12 rats received saline instead of PSK (non-PSK group). Five days after inoculation of tumor cells, the right hind limb of each rat was amputated under ethylether anesthesia. Four animals each were sacrificed on the day before operation (preop. day 1) as well as 1 and 7 days after surgery (postop. days 1 and 7), and blood samples were obtained. When animals were killed on postop. day 7, the right adrenal gland and the spleen were also harvested. The adrenal gland was weighed and the organ to body weight ratio was calculated. Twelve normal untreated rats served as the control (cont. group).

2) Determination of plasma ACTH, cortisol and serum IAP

Using the blood samples, the plasma ACTH concentration was measured by an immunoradiometric assay (IRMA) and the plasma cortisol concentration was measured by a radioimmunoassay (RIA). The serum IAP concentration was also measured by the single radial immunodiffusion (SRID) method.

3) Preparation of spleen cell and MTT assay

Spleens obtained on postop. day 7 were washed in phosphate buffer saline (PBS), and cut into fragments with small scissors. To these spleen fragments was added 5 ml of RPMI-1640 medium with 10% fetal calf serum (FCS). Then the mixture was filtered, and spleen cells were harvested from the filtrate using LYMPHOLYTE-M (Cedarlane Lab, Lim, Canada). After washing in PBS, the cells were suspended in RPMI-1640 medium with 10% FCS and adjusted to a concentration of 1×10^6 cells/ml. A 100 μl aliquot (1×10^5 cells) was added to each well of a 96-well microtest plate (Coster, USA). After incubation for 120 hours at 37℃ in a 5% CO_2 atmosphere, a 50 μl aliquot of MTT [3- (4, 5-dimethyl-thiazol-2-yl) -2, 5-diphenyl tetrazolium bromide] solution (2 mg/ml in PBS) was added to each well, and the plate was incubated for another 5 hours as before. After centrifugation for 15 minutes at 1,500 rpm, the supernatant was removed from the wells, and 100 μl of dimethyl sulfoxide (DMSO) was added to the cells remaining in each well. The plate was placed on a plate shaker, and the cells were agitated for 30 minutes to dissolve the formazan grains, after which the optical density (OD) of each well was measured at 570 nm with a microplate reader (BIO-RAD, USA).

3. Experiment II

PSK administration and surgical treatment

After inoculation of tumor cells, 12 rats were divided into two groups; 6 rats received oral PSK (1,000 mg/kg daily) for 5 days (PSK group) and the other 6 rats received 0.9% NaCl instead (non-PSK group), as experiment I. All animals underwent amputation of the right hind limb under ethylether anesthesia 5 days after tumor cell inoculation. They were followed postoperatively to calculate the mean survival period (days).

4. Statistical analysis

In experiment I, results are given as the mean ± SD. All spleen cell proliferation studies were at

least run in triplicate, for both the experimental and the control groups. Statistical analyses were performed by Student's t-test. In experiment II, survival was assessed by the mean survival period, and the significance of differences was evaluated by the generalized Wilcoxon test. All p-values presented are two-sided and differences were considered significant at $p< 0.05$.

Results

1. Experiment I

1) Plasma ACTH

On preop. day 1, in both the non-PSK and PSK groups, the ACTH level tended to be higher than in the cont. group ($p<0.1$). On postop. day 1, the level in the non-PSK group was significantly higher than in the cont. group ($p<0.05$). On postop. day 7, the level was higher in the non-PSK group than in the cont. group, but the difference was not significant. The PSK group showed a significantly lower level than the non-PSK group on postop. day 1 ($p<0.05$) (Fig. 1).

2) Plasma cortisol

On preop. day 1, the cortisol level was significantly higher in both the non-PSK and PSK groups than in the cont. group ($p<0.05$). On postop. day 1, the level was significantly higher in the non-PSK group than in the cont. group ($p<0.05$). On postop. day 7, the non-PSK group showed a significantly higher level than the cont. group ($p<0.05$). The PSK group tended to have a lower level than the non-PSK group on postop. day 1 ($p<0.1$) and this decrease became significant on postop. day 7 ($p<0.05$) (Fig. 2).

3) Adrenal weight ratio

On postop. day 7, the ratio was significantly higher in the non-PSK group than in the cont. group ($p<0.01$), while the ratio was significantly lower in the PSK group than in the non-PSK group ($p<0.05$) (Fig. 3).

4) Serum IAP

On preop. day 1 and postop. day 1, in both the non-PSK and PSK groups, IAP levels were significantly higher than in the cont. group ($p<0.001$). On postop. day 7, the non-PSK group had a significantly higher level than the cont. group ($p<0.05$). The PSK group showed a significantly

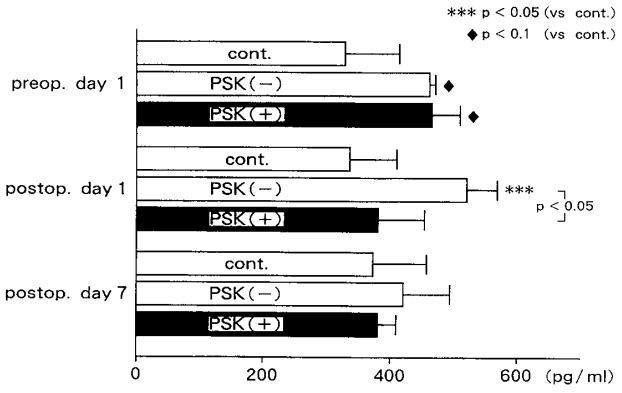

Fig. 1 Plasma ACTH concentration

On preop. day 1, the plasma ACTH concentration (pg/ml) was 326 ± 90 in the cont. group, 465 ± 5 in the non-PSK group, and 467 ± 39 in the PSK group. On postop. day 1, the corresponding concentrations were 330 ± 80, 518 ± 47, and 379 ± 73. On postop. day 7, the respective concentrations were 368 ± 92, 423 ± 77, and 372 ± 45. PSK suppressed the oversecretion of ACTH under surgical stress.

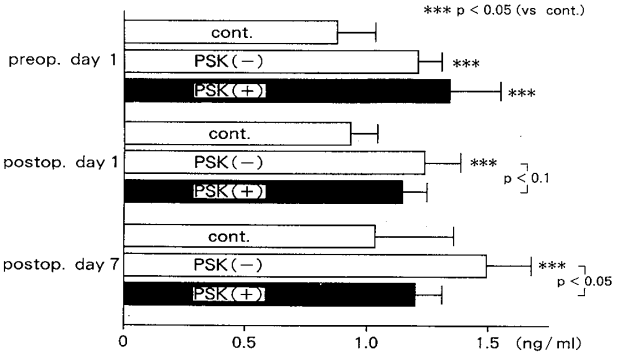

Fig. 2 Plasma cortisol concentration

On preop. day 1, the plasma cortisol concentration (ng/ml) was 0.87 ± 0.15 in the cont. group, 1.20 ± 0.10 in the non-PSK group, and 1.33 ± 0.21 in the PSK group. On postop. day 1, the respective concentrations were 0.90 ± 0.10, 1.23 ± 0.15, and 1.13 ± 0.10. On postop. day 7, the respective concentrations were 1.03 ± 0.32, 1.47 ± 0.21, and 1.20 ± 0.10. PSK suppressed the oversecretion of cortisol under surgical stress.

lower level than the non-PSK group on postop. days 1 and 7 ($p<0.05$) (Fig. 4).

5) MTT assay

MTT assay was performed with spleen cells obtained from postop. day 7. The value obtained in the non-PSK group was significantly lower than that for the cont. group ($p<0.05$), while the value obtained in the PSK group was significantly higher than that for the non-PSK group ($p<0.01$). (Fig. 5).

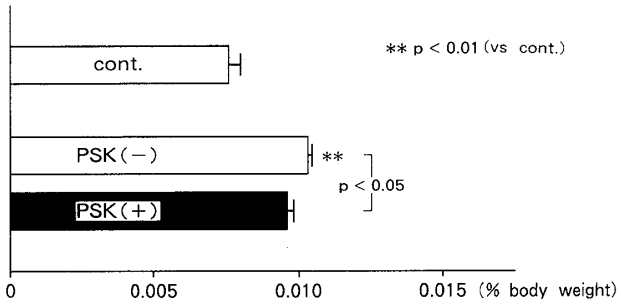

Fig. 3 Right adrenal weight ratio on postop. day 7
The right adrenal gland/body weight ratio was 0.0074 ± 0.0014 in the cont. group, 0.0112 ± 0.0008 in the non-PSK group, and 0.0092 ± 0.0001 in the PSK group. PSK corrected adrenal overactivity under surgical stress.

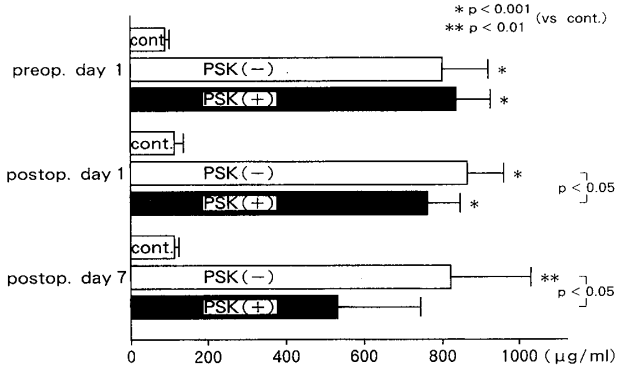

Fig. 4 Serum IAP level
On preop. day 1, the serum IAP level (μg/ml) was 82 ± 10 in the cont. group, 796 ± 120 in the non-PSK group, and 832 ± 93 in the PSK group. On postop. day 1, the respective concentrations were 111 ± 21, 855 ± 108, and 762 ± 98. On postop. day 7, the respective concentrations were 108 ± 4, 826 ± 385, and 513 ± 216. PSK suppressed the overproduction of IAP under surgical stress.

2. Experiment II

Effect of PSK on survival

In both the non-PSK and PSK groups, all rats died as a result of tumor metastasis after amputation of the right hind limb. The survival curves of rats from both groups are shown in Fig. 6. Although the postoperative survival time was longer in the PSK group, the difference was not statistically significant.

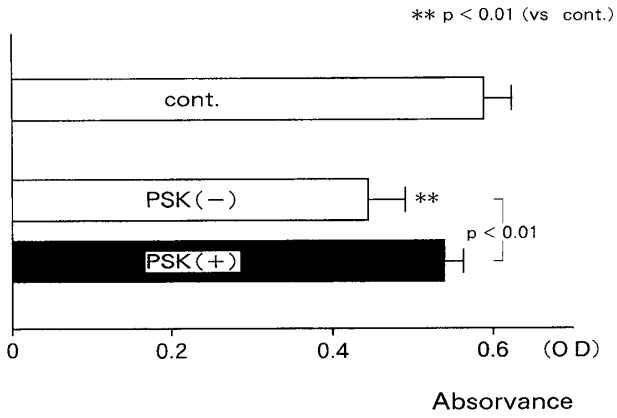

Fig. 5 MTT assay performed with spleen cells obtained on postop. day 7
The OD 570 value was 0.58 ± 0.01 in the cont. group, 0.46 ± 0.04 in the non-PSK group, and 0.54 ± 0.02 in the PSK group. The proliferative activity of spleen cells was reduced by surgical stress and was improved by treatment with PSK.

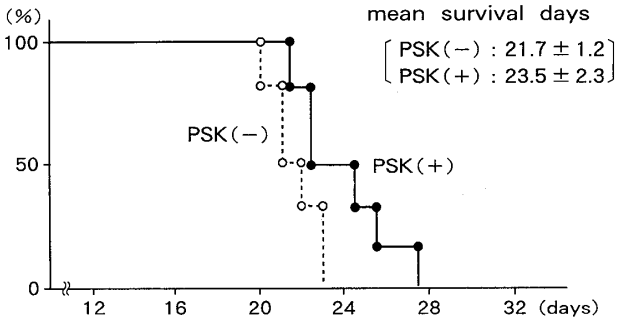

Fig. 6 Effect of PSK preoperative administration on survival of tumor-bearing rats
The mean survival period was 21.7 ± 1.2 days in the non-PSK group, while it was 23.5 ± 2.3 days in the PSK group. Although the PSK group had a long survival, the difference was not statistically significant.

Discussion

When the body is exposed to surgical stress, the endocrine system secretes various hormones in a response mediated by the pituitary-adrenal axis and the autonomic nervous system[18].

The blood levels of inflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor (TNF), IL-6, and IL-8, also increase in response to surgical stress[19], and thereby cause an increase of so-called acute phase reactants, including C-reactive protein (CRP) and immunosuppressive acidic protein (IAP).

Suppression of cellular immunity is one of the surgical stress-induced biological responses of the hosts[1)~6)]. A variety of hormones (particularly adrenal corticosteroids), cytokines, and acute phase reactants are involved in the complex mechanism by which immunosuppression is induced.

Experiment I was performed using an animal model which closely resembled the situation encountered in clinical practice. KDH-8 tumor cells were inoculated into the right hind limb of rats and amputation was done 5 days later.

First, the effects of the operation itself and anesthesia (i. e., surgical stress) were examined by comparison of the cont. group with the non-PSK group.

Investigation of the pituitary-adrenal axis showed that plasma ACTH and cortisol concentrations were increased on preop. day 1 as a result of the tumor-bearing state. On postop. day 1, during the adrenergic corticoid phase[20] of the response to surgical stress, the plasma levels of both hormones were markedly increased. On postop. day 7, the ACTH level was decreased to almost the control value, while cortisol was increased further. In addition, the adrenal glands showed an increase in weight, suggesting overactivity. During surgical stress, many stimuli are transmitted to the diencephalon, leading to the liberation of corticotropin-releasing factor (CRF) from the hypothalamus. This factor stimulates the anterior lobe of the pituitary and enhances ACTH secretion. An increase of circulating ACTH mediates cortisol secretion from the adrenal cortex[21]. Six hours after amputation of the right hind limb, plasma ACTH was reported to decrease to the preoperative level, whereas plasma cortisol remains elevated for more than 3 days postoperatively[22]. The results of the present study were in agreement with such data. It is well known that cortisol has an immunosuppressive effect, and reported that it suppresses the response of lymphocytes to phytohemagglutinin (PHA), a T cell mitogen, and the response of T cells to IL-2[23].

In addition, the effects of surgical stress on the serum IAP level were investigated. IAP is an α_1-acid glycoprotein-like acid protein that was originally purified from cancer ascites[24]. IAP is a non-specific immunosuppresive factor[25)26)], and two mechanisms are known to be involved in its production. One is associated with tumor progression[27] and the other is production as an acute phase reactant during acute inflammation. IAP was increased by the tumor-bearing state on preop. day 1, and it increased further in response to surgical stress on postop. days 1 and 7. IAP as an acute phase reactant is produced by macrophages, neutrophils, and hepatocytes in response to stimulation by TNF and IL-6[28)29)]. IL-1 and TNF are induced first in response to surgical stress, after which IL-6 and IL-8 are induced. These cytokines mediate various biological responses[19)30)]. The postoperative increase of the serum IAP level observed in the present study can be regarded as one of the biological responses to surgical stress.

We found that the plasma cortisol and serum IAP levels remained increased for more than 7 days postoperatively. The OD 570 value determined in the MTT assay was evidently reduced for spleen cells obtained on postop. day 7. The

MTT assay assesses the mitochondrial reducing activity of cells, which is related to the mitochondrial energy level and reflects the cellular proliferative activity[31]. Consequently, this result suggests that the function of immunocompetent cells should be suppressed on postop. day 7 in rats undergoing hind limb amputation.

These results suggested that secretion of high levels of adrenal corticosteroids such as cortisol and overproduction of IAP may be heavily involved in the suppression of cellular immunity induced by surgical stress.

When malignant tumors are treated surgically, the resultant stress may cause cellular immunosuppression that may assist the residual cancer cells to grow and metastasize[8)~11)]. Preoperative treatment with BRMs has been tried in an attempt to minimize such immunosuppression[12)~17)].

PSK is a protein-bound polysaccharide extracted from Coriolus, which has been widely used as a BRM for the treatment of cancer patients in Japan. PSK is known to have the following actions : ① enhancement of various host immune responses[31)~33)], ② modulation of the expression and production of cytokines[34)35)], and ③ competitive inhibition of substances that produce immunosuppression[36)37)].

Therefore, we administered PSK to rats prior to surgical resection of cancer and investigated its preventive effect on cellular immunosuppression induced by surgical stress. In the PSK group, the secretion of ACTH and cortisol and the production of IAP were decreased on postop. day 1 relative to the levels in the non-PSK group with cortisol and IAP production remaining suppressed even on postop. day 7. On postop. day 7, adrenal weight was decreased, indicating correction of the overactivity of the gland under surgical stress. In addition, the proliferative activity of spleen cells was improved and immunocompetent cell function was normalized. PSK was thus effective in suppressing the excessive secretion of cortisol and overproduction of IAP under surgical stress. As a result, suppression of cellular immunity was prevented.

Using animal model of cancer produced by inoculation of colon 26 tumor cells into the spleens of mice, Sugiyama et al[38] found that preoperative treatment with PSK could prevent overproduction of IL-6 in response to surgical stress, and also inhibited liver metastasis. Interestingly, IL-6 mediates the production of IAP.

It is difficult to provide a clear explanation of the mechanism by which PSK produced the effects observed in the present study. In addition to the three actions described previously, this BRM regulates the secretion of adrenal corticosteroids. It has been suggested that production of IAP is also controlled by the regulation of cytokine production. Therefore, these actions of PSK may prevent the suppression of immunocompetent cell function.

Experiment II was designed to study the association between the prevention of immunosuppression under surgical stress by PSK and the prognosis of cancer. Survival was prolonged in animals receiving PSK, although the improvement was not statistically significant. Thus, no conclusive evidence was obtained with respect to the effect of PSK on the prognosis. It therefore appears necessary to continue this study in more rats to demonstrate a conclusive difference.

Acknowledgements

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手術侵襲による細胞性免疫能の低下とそれに対するPSKの効果について

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手術侵襲による生体反応の一つに細胞性免疫能の低下がある．生体に手術侵襲が加われば，内分泌系ホルモン，サイトカイン，急性相反応物質などが産生されて多彩な反応が引き起こされ，それらの複雑な作用により細胞性免疫能は低下する．著者らは，その発現のメカニズムとそれに対するPSK（protein-bound polysaccharide Kureha）の術前投与の効果について実験的に検討した．まずメカニズムについて，手術侵襲によって副腎皮質ホルモンのコルチゾールや急性相反応物質である免疫抑制性酸性蛋白が血液中に放出されることが確認された．これら免疫抑制因子によって宿主の免疫担当細胞の機能は傷害され，細胞性免疫能は低下すると考えられる．次にPSKの効果についてみると，その術前投与によってコルチゾールや免疫抑制性酸性蛋白の過剰な産生が抑えられ，その結果，手術侵襲による細胞性免疫能の低下も防止できると考えられた．がんを手術する場合，こうした術中から術後の細胞性免疫能低下を防止することは腫瘍の増殖や転移形成との関連から重要であるが，biological response modifier（BRM；生物学的応答調節剤）の一つであるPSKの術前投与によって防止しうることが示唆された．