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Cancer cachexia and depressive states: a neuro-endocrine-immunological disease?

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Abstract

Plasma 5-hydroxytryptamine (serotonin), tryptophan, neopterin and cortisol levels were measured in patients with depreive cancer cachexia and in healthy controls during the same time period. Patients with advanced cancers had significantly raised neopterin, a marker of endogenous gamma-interferon (IFN-γ) production, and cortisol values, but decreased serotonin and tryptophan levels. Much work has been done to elucidate the poible role of serotonin in depreive states. IFN-γ induces a high level of indoleamine dioxygenase (IDO), a tryptophan degrading enzyme, and high cortisol levels induce high tryptophan oxygenase activity, which in turn increases metabolism along the tryptophannicotinic acid pathway. These results suggest that persistent immune activation and intense adrenal activity occur in patients with cancer cachexia, resulting in disorders involving tryptophan metabolism followed by depreion in cancer cahexia.

KEYWORDS: cancer cachexia, neuro-endocrine-immune interactio, serotonin, neopterin, cortisol

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Brief Note

Cancer Cachexia and Depressive States: A Neuro-Endocrine-Immunological Disease?

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Plasma 5-hydroxytryptamine (serotonin), tryptophan, neopterin and cortisol levels were measured in patients with depressive cancer cachexia and in healthy controls during the same time period. Patients with advanced cancers had significantly raised neopterin, a marker of endogenous gamma-interferon (IFN-γ) production, and cortisol values, but decreased serotonin and tryptophan levels. Much work has been done to elucidate the possible role of serotonin in depressive states. IFN-γ induces a high level of indoleamine dioxygenase (IDO), a tryptophan degrading enzyme, and high cortisol levels induce high tryptophan oxygenase activity, which in turn increases metabolism along the tryptophan-nicotinic acid pathway. These results suggest that persistent immune activation and intense adrenal activity occur in patients with cancer cachexia, resulting in disorders involving tryptophan metabolism followed by depression in cancer cahexia.

Key words: cancer cachexia, neuro-endocrine-immune interaction, serotonin, neopterin, cortisol

There is a lot of modern evidence that malignant diseases sometimes result in depressive states that are of an endogenous nature, not caused by gross brain damage, which become apparent after the discovery of the malignancy (1-3). However, the mechanisms by which depressive symptoms in cancer cachexia are mediated have not yet been clearly elucidated. Much work has been done to elucidate the possible role of biogenic amines, including serotonin, in depressive illness. Since 1954, there has been a succession of observations and reports suggesting that depletion or reduced activity of monoamines may cause depressive illness (4-12). There have been extensive investigations of the biochemical aspects of the amine hypothesis of depression. Although it is hazardous to attempt to simplify the matter, it is probably safe to say that some depressions are associated with reduced activity of biogenic amines in the brain. The amines which have been studied are norepinephrine, dopamine and serotonin. There may be different biochemical forms of depressive illness, caused by decreased activity of different amines, the principal amines involved in the central nervous system being serotonin.

Tryptophan is an essential and indispensable amino acid required for the biosynthesis of serotonin and nicotinic acid. Intake of less than the required amount promptly results in a negative nitrogen balance and significant reduction in tryptophan metabolite levels in the blood. Because tryptophan is released from the breakdown of body protein during tryptophan deprivation, it is probably not possible to decrease serum tryptophan below a certain level as long as body protein pools are available for breakdown. Metabolism of tryptophan to the nicotinic acid pathway is initiated in liver by the classical tryptophan dioxygenase pathway. Osamu Hayaishi's excellent paper reported the presence of another distinct nonhepatic enzyme able to form kynurenin from tryptophan. They named this enzyme indoleamine 2,3-dioxygenase (IDO). Most exciting were reports that IDO was highly induced by stimulation of the immune system by IFN-γ (13-16). In recent years, neopterin, one of factors released from activated macrophages, has been identified as a new

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biochemical marker for the activation of the cellular immunity. IFN-γ produced by T-cells activates macrophages, which in turn release neopterin. Thus, neopterin elevation directly points to stimulation of macrophages and indirectly to T-cell activation, and therefore demonstrates activation of the cellular immune system or increased endogenous IFN-γ production (17–19).

In the following, we will describe a possible association between the cellular immune system, disturbed tryptophan metabolism and psychiatric symptoms in patients with cancer cachexia.

Materials and Methods

Twenty-eight male and 28 female patients, aged 28 to 88 years, with a median age of 58 years, suffering from gastrointestinal cancers were used as subjects in this study. Patients were serologically and/or histologically confirmed as having metastasizing and/or recurrent cancers. These cancers were unresectable and noncurable malignant solid tumors. All patients had cachectic symptoms, such as weight loss, appetite loss, anemia, pain and/or depressive states. Venous blood samples were collected at 8:00 a.m. and no patients were undergoing concomitant therapy with steroids and/or other drugs which may affect the immune system. Plasma neopterin, cortisol, tryptophan and serotonin were measured in these patients and in a group of healthy controls during the same time period. Neopterin (6-D-erythro- [1′,2′,3′-trihydroxy-propyl] -pterin) concentrations in plasma were measured by high pressure liquid chromatography (HPLC) (20). Radioimmunoassays, using Gamma coat ^{125}I cortisol RIA kit (Travenol Co. Ltd., Tokyo, Japan), were used for the quantitative assay of plasma cortisol levels. Plasma tryptophan levels were measured by aminoacids autoanalyzer (Hitachi 835-50, Japan). For plasma serotonin, we used reversed phase, ion-pair high pressure liquid chromatography (HPLC) with electrochemical detection (21). Data were reported as mean + SE and analyzed by unpaired Student's-t test, with a level of $P < 0.05$ considered to be statistically significant.

Results and Discussion

Patients with advanced cancers had significantly raised neopterin and cortisol values, whereas those had significantly decreased tryptophan and serotonin levels in comparison with healthy controls (Table 1). Decreased tryptophan could result from increased activity of IDO which is induced by IFN-γ and degrades tryptophan to form kynurenine, which then is further metabolized. Increased concentrations of neopterin in patients reflect chronic immune stimulation. Large quantities of neopterin are released by human macrophages on stimulation with IFN-γ *in vitro*. Release of neopterin, therefore, is paralleled by a significant degradation of tryptophan (13–16). Elevated plasma corticosteroid levels induce a high activity of tryptophan oxygenase, which in turn increases metabolism along the tryptophan-nicotinic acid pathway (22–24). Thus, reduced tryptophan levels are very likely to result from persistent immune activation and intense adrenal activity through high activities of IDO and tryptophan oxygenase, and low tryptophan concentrations may explain decreased plasma serotonin levels (Fig. 1).

To our knowledge, this is the first report of plasma serotonin levels in patients with cancer cachexia. Over 90 % of blood serotonin is stored in platelets, considered as a possible parallel parameter for serotoninergic neurones (25). In this context, it is interesting to note that plasma serotonin has been reported to be decreased in other long-term latent virus-associated neurological animal and human diseases including scrapie, Creutzfeldt-Jakob disease (CJD) (26, 27) and AIDS (28, 29). There are several possible explanations: impaired platelet and/or

Table 1 Plasma levels of neopterin, cortisol, tryptophan and serotonin in patients with advanced cancers and normal controls

	Neopterin (pmol/ml)	Cortisol (μg/dl)	Tryptophan (nmol/ml)	Serotonin (μg/dl)
Cancer	20.2 ± 23.7* (n = 56)	14.0 ± 3.3** (n = 15)	33.1 ± 10.7** (n = 28)	7.6 ± 4.5** (n = 15)
Control	3.7 ± 1.2 (n = 10)	8.7 ± 3.1 (n = 30)	60.5 ± 9.9 (n = 50)	14.9 ± 4.1 (n = 27)

Values are mean ± SD. Statistical analysis between cancer patients and normal controls was performed by Student's t-test, with a level of $P < 0.05$ or 0.01 considered to be statistically significant. *$P < 0.05$ and **$P < 0.01$ *vs.* control.

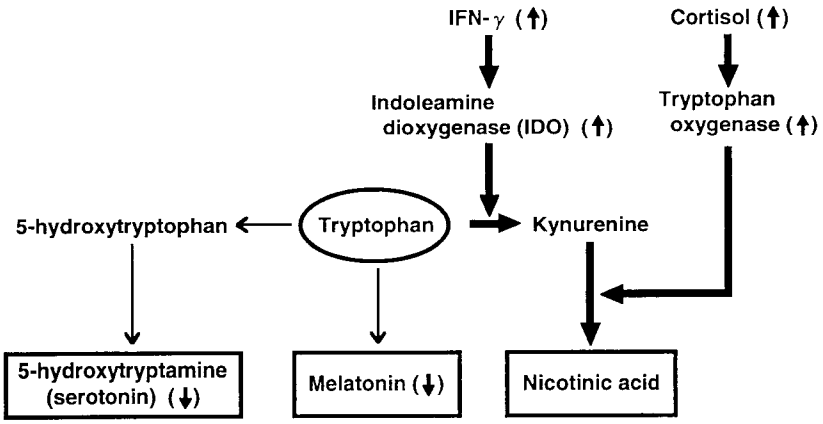

Fig. 1 Biochemistry of tryptophan metabolism in cancer cachexia

lymphocyte serotonin uptake, as already reported for scrapie-infected sheep and CJD patients (26, 27); increased serotonin catabolism, as suggested by the presence of high levels of conjugated serotonin in the supernatants of scrapie-infected neuroblastoma cells (26, 27); a decrease of serotonin biosynthesis by enterochromaffin cells, as might be infered from the recent detection of HIV in bowel biopsy specimens from AIDS patients (28, 29).

Increased neopterin concentrations and the relevance of IDO activation can be also observed in HIV-1 seropositive patients. Impaired tryptophan metabolism and reduced availability of serotonin could be involved (30, 31). In addition, a significant correlation between decreased tryptophan and neuropsychological disturbances such as dementia and polyneuropathy in HIV-1 seropositive patients has already been demonstrated (32-34). However, it remains to be shown whether neurotoxic tryptophan metabolites or altered availability of serotonin, or both together, contribute to neuropsychological deterioration in patients. Both metabolic abnormalities, however, may result from the chronic challenge of cell-mediated immunity and concomitant release of cytokines in patients with long-lasting illness as such as HIV-1 infection and cancer cachexia.

In conclusion, this study suggests that cancer cachexia is a neuro-endocrine-immunological response against tumors and its pathogenesis has an essential similarity to that of AIDS.

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