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ORIGINAL ARTICLE

Psychooncology and cancer progression-related alterations of pleasure-associated neurochemical system: Abnormal neuroendocrine response to apomorphine in advanced cancer patients

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Abstract

OBJECTIVES: The clinical approach of the Psychoncology is generally limited to the investigation of the only psychological status of cancer patients, without taking into consideration the well demonstrated cancer progression-related psychoneuroendocrine alterations, namely consisting of a progressive decline in the pineal endocrine function and an anomalous activity of brain opioid system. The endocrine response to apomorphine, a dopaminergic agent, has been proven to reflect the dopaminergic sensitivity, which would be involved at least in part in pleasure-related neurochemical mechanisms. The present study was performed to analyze the endocrine response to apomorphine in metastatic cancer patients, as a preliminary approach to the investigation of pleasure-related neuroendocrine mechanisms in human neoplasms. **MATERIALS & METHODS**: The study included 10 metastatic cancer male patients and 6 male volunteers as a control group. Apomorphine was given orally at 0.01 mg/kg body weight in the morning, and venous blood samples were collected before, and at 20, 60 and 120 minutes after apomorphine administration. The endocrine analysis consisted of the measurement of serum levels of GH, PRL and cortisol. **RESULTS**: All cancer patients presented alterations involving one or more endocrine responses to apomorphine. GH and cortisol mean levels after apomorphine were significantly higher in controls than in cancer patients, whereas no substantial difference occurred in those of PRL. **CONCLUSIONS**: This preliminary study, by showing an altered endocrine response to apomorphine in metastatic cancer patients, would suggest that cancer progression may be associated with an altered dopaminergic sensitivity. Because of the involvement of the dopaminergic system in pleasure-related neurochemical mechanisms, this finding would demonstrated that the decline in the perception of pleasure with cancer progression may depend not only on psychological factors, but also, at least in part, on psychochemical alterations occurring during the clinical course of the neoplastic disease.

Introduction

It has been shown that cancer onset and progression are associated with evident changes in the neurobiochemistry of brain, whose correction may opposite the malignant transformation and diffusion [1]. Therefore, the neuroendocrine alteration associated with the development of cancer would be essential for tumor onset itself. This finding would depend on the fact that both cell proliferation and antitumor immunity are under a psychoneuroendocrine regulation, which may promote or counteract tumor development and progression [2]. Stress and depression are associated with enhanced tumor frequency [3], and this evidence would depend at least in part on an increased brain opioid tone, since the administration of opioid antagonists has been proven to abrogate stress-induced promotion of cancer growth in experimental conditions [4]. The opioid agents would play a promoting effect on cancer growth by inhibiting the generation of an effective anticancer immune reaction [5]. At the other side, pleasure and spiritual amplification of the consciousness opposite cancer growth by activating brain structures provided by anticancer immunostimulatory activity, such as pineal gland and gabaergic system [6]. In addition, the dopaminergic pathway has appeared to play a fundamental role in the generation of pleasure and consciousness expansion [2]. The administration of apomorphine, a direct-acting dopamine agonist, has appeared to be able to predict individual different dopaminergic sensitivity [7]. Moreover, apomorphine administration induces important neuroendocrine effects in healthy conditions, consisting of stimulation of GH, LH and cortisol secretions and inhibition of PRL release [8,9] addition, apomorphine has appeared to induce penile erection by acting at central areas [10]. Finally, apomorphine has been proven to exert direct antiproliferative antitumor activity against several tumor histotypes, including gliomas, meningiomas, melanoma, colorectal cancer, bladder carcinoma and haematologic malignancies [11–13], by confirming that the biochemistry of pleasure plays an anticancer activity [2]. In human diseases characterized by important brain neuroendocrine anomalies, such as schizophrenia, the neuroendocrine response to apomorphine has been shown to be altered [14]. In particular, schizophrenia-associated altered response to apomorphine has appeared to consist of reduced GH and cortisol increase and diminished PRL decline [14].

Advanced cancer patients have been also shown to present evident neuroendocrine alterations, namely a diminished pineal function and an enhanced opioid tone [2], whereas, at present, there are no data about the neuroendocrine response to apomorphine in human neoplasms, which are also characterized by changes in the sexual behaviour [2] that cannot be simply explained in terms of psychological factors. On this basis, a study was planned to investigate the neuroendocrine effects of apomorphine in cancer patients, in an attempt to further characterize cancer-related neuroendocrine anomalies.

Materials and mtehods

The study included 10 male subjects suffering from metastatic solid neoplasms and 6 healthy male volunteers as a control group. Patients under chronic therapy with endocrine agents, steroids, opioids or anti-dopaminergic agents were excluded from the study. Tumor histotypes of cancer patients were, as follows: renal cell carcinoma: 4; colorectal cancer: 3; non small-cell-lung cancer: 2; pancreatic cancer: 1. Dominant metastasis sites were, as follows: bone: 1; lung: 4; liver: 3; liver plus lung: 2. The experimental protocol and its biological significance were explained to each patient and healthy subject, and written consent was obtained. Apomorphine was given orally at 0.01 mg/kg body weight at 8.00 A.M. after an overnight fast, and venous blood samples were collected through an indwelling catheter before apomorphine administration, and at 20, 60 and 120 minutes from apomorphine administration. In each blood samples, we evaluated serum levels of PRL, GH and cortisol the double antibody RIA method and commercially available kits. Data were reported as mean + SE, and statistically analyzed by the Student's *t-test* and the analysis of variance, as appropriate.

Results

As expected, cortisol and GH serum levels increased in response to apomorphine in all healthy controls, whereas those of PRL decreased. In contrast, alterations involving one or more endocrine responses to apomorphine were observed in all cancer patients. A lack of cortisol increase occurred in 7/10 patients. No GH enhancement after apomorphine administration was observed in 8/10 patients. Finally, a normal PRL decline in response to apomorphine occurred in 7/10 patients, whereas no PRL decrease was seen in the remaining 3 patients. Changes in mean serum levels of PRL, GH and cortisol observed after apomorphine in controls and in cancer patients were illustrated in Figures 1, 2 and 3, respectively. GH and cortisol mean levels after apomorphine were significantly lower in cancer patients than in healthy controls. Finally, PRL mean concentrations after apomorphine were higher in patients than in controls, without, however, statistically significant differences. No apomorphine-related subjective or objective toxicity occurred during the study.

Discussion

This study, which has been performed to analyze the dopaminergic sensitivity [7] in cancer patients as an aspect of pleasure-related mechanisms, would suggest that cancer progression may be associated with psychochemical dysfunctions. In fact, the evidence of an altered neuroendocrine response to apomorphine in metastatic cancer patients, as shown by the present study, would reflect the existence of an anomalous dopaminergic sensitivity. Then, because of the importance

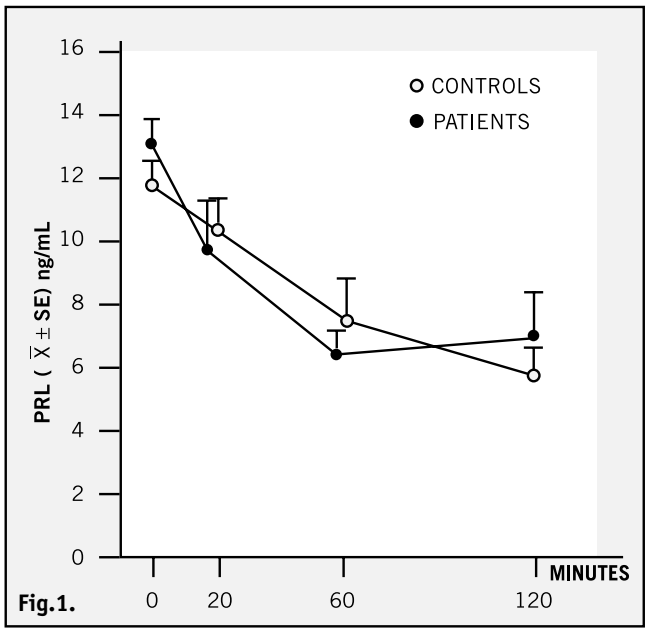

Fig.1.

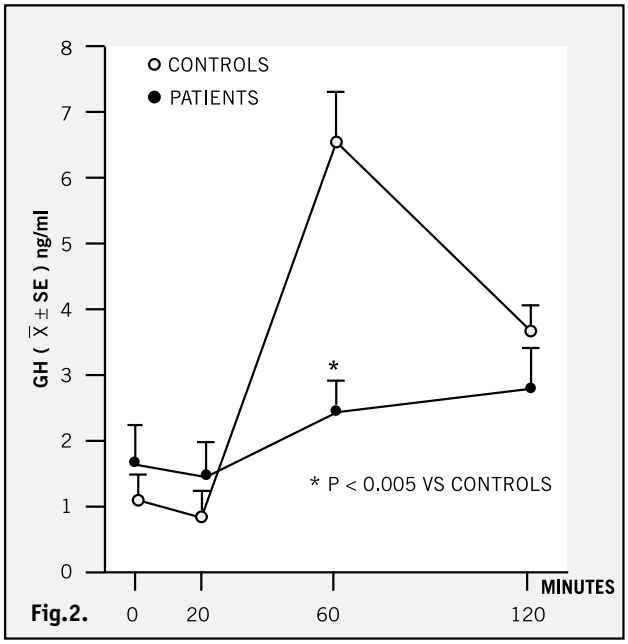

Fig.2.

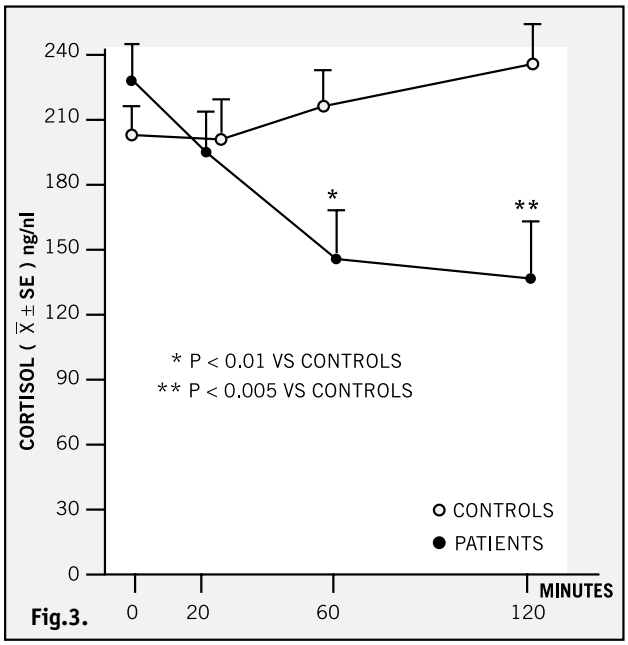

Fig.3.

Fig.1: Changes in mean serum levels of PRL after apomorphine in cancer patients and in controls.

Fig.2: Changes in mean serum levels of GH after apomorphine in cancer patients and in controls.

Fig.3: Changes in mean serum levels of cortisol after apomorphine in cancer patients and in controls.

of the dopaminergic system in inducing the perception of pleasure [1,2], the diminished capacity of pleasure perception occurring during the neoplastic progression would not represent only a simple psychological consequence of the neoplastic disease, but it would depend at least in part on an altered psychoneurochemical status. Moreover, cancer-related neurochemical alterations do not seem to simply represent an epiphenomenon. In fact, in experimental conditions it has been demonstrated that the pharmacological or electrophysiological correction of cancer development-related changes in the biochemistry of brain, namely those involving the dopaminergic system, may counteract the onset of cancer itself [2]. However, according to the advances in the psychoneuroendocrine knowledge [15], it has to be taken into consideration that the dopaminergic system, either alone or in relation to brain opioid system, would not be the only functional neurochemical structure involved in the regulation of pleasure, and in particular it has been recently demonstrated the existence of brain cannabinergic system [15], which seems to play a fundamental role in regulating pleasure-related neurochemical mechanisms and whose functionless could be abnormally decreased in the advanced cancer patients. At present, no study has been carried out to explore the functionless of the endogenous cannabinoid system in cancer. However, because of the well documented existence of a link between cannabinoid substances and pineal endocrine function [16], the progressive decline in the pineal activity with cancer progression could induce a concomitant decline in the functionless of the cannabinergic system [2,6]. In any case, further studies will be needed to better define the neuroendocrine alterations involving pleasure-related neurochemical mechanisms in relation to either the clinical stage of the neoplastic disease, or the different

tumor histotypes. Moreover, successive studies, by evaluating the neuroendocrine status of cancer patients before and after an effective therapy of their disease, will be needed to establish whether the control of cancer progression may be associated with a normalization of pleasure-related psychoneuroendocrine structures, whose function less may influence both quality of life and immune reactivity of cancer patients. If further studies will confirm the existence of cancer progression-related alterations of the neurobiochemistry of pleasure, the eventual use of cannabinoids in the advanced cancer patients would not represent only a palliative treatment, but it could constitute a pharmacological therapy carried out to correct cancer-induced alterations of the neurochemical pathways of pleasure. On the same way, dopaminergic agonists, such as apomorphine itself, could be successfully used to improve the perception of pleasure in the advanced cancer patients, and this proposal is justified by the fact that apomorphine has appeared to exert potential oncostatic effects, at least in experimental conditions [11–13].

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