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Depression and Cancer: A Role for 5-HTTLPR and SSRI Antidepressant Drugs?

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ABSTRACT: Before tumor diagnosis, stressful life events experienced by women with breast cancer are associated with the later development of depressive conditions; 5-HTTLPR does not play any significant role. After tumor diagnosis, mental adaptation to cancer is characterized in women with early breast cancer by anxious preoccupation which spontaneously decreases at follow-up; the reduction is significant only in the carriers of the "l/l" 5-HTTLPR genotype. Antidepressants act on depression and mental adaptation to the disease, and the response is genotype dependent. 5-HTTLPR has therefore a role in psycho-oncology, permitting the identification of patients with greater need of support (carriers of "s/s" genotype), and in the case of drug treatment allowing the personalized choice of the drug (benzodiazepines for treating anxiety, or non-SSRI ADs for treating depression in "s/s" patients). Altogether, these data are in agreement with the more recent non-oncological reviews, showing a real, though small, effect of 5-HTTLPR on environmental adversity and the action of SSRI antidepressants.

KEY WORDS: depression; stress; mental adaptation to cancer; serotonin transporter polymorphism; 5-HTTLPR; antidepressant drugs; SSRI

I. STRESS AND CANCER

It is widely acknowledged that stress may affect cancer incidence and progression, through the participation of a circuit of effectors, beginning with the elaboration of psychological and physiological stimuli and leading to neurovegetative and neuroendocrine changes capable of negatively affecting the host-tumor relationships.[1]

Metastasis is crucial for tumor malignancy, and therefore we examined the effects of experimental stressors on spontaneous tumor spread: Several paradigms of psychological stress (such as physical restraint and spatial disorientation) specifically increased metastasis in mice bearing solid malignant tumors, in a way unrelated with, and also in the absence of effects on, the primary tumor.[2] When the same stressors were combined with cyclophosphamide chemotherapy,

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the remarkable effects of this antitumor drug were sharply attenuated, and its curative action was abolished.[3]

These original observations are consistent with the large number of observations, for which critical review and meta-analysis show that stressful life experiences are related in the clinic to decreased cancer survival and increased mortality.[4]

II. MENTAL ADAPTATION TO CANCER AND DEPRESSION

The communication of the diagnosis of cancer is a stressful event, to which different subjects will mentally adapt in different ways. When women with breast cancer were analyzed with Mental Adjustment to Cancer (MAC) scale and Hospital Anxiety and Depression Scale (HADS), there was a significant increased risk of relapse or death in women with high scores of *depression* (HAD-D) and of MAC *hoplessness-helplessness* (MAC-HH).[5] Stress and depression are related in psychiatric conditions, and they were found to be related also in oncology, including their negative effects on immune competence of the host.[6] In our experience, a high correlation was found between MAC-HH and *anxious preoccupation* (MAC-AP), with HAD-D and *anxiety* (HAD-A) in early breast cancer patients: In patients with advanced tumors *HAD-D* also negatively correlated with MAC *fighting spirit* (MAC-FS).[7]

III. 5-HTTLPR, DEPRESSION, AND MENTAL ADAPTATION TO CANCER

A paper by Caspi and colleagues in 2003 attracted wide interest, since it showed that a polymorphism with high penetrance and significant functional relevance, consisting in the insertion-deletion of 44 bp in the promoter region of serotonin transporter SERT (5-HTTLPR), influenced the depressive conditions of individuals experiencing stressful life events, with a significant gene×environment interaction. In this study, the carriers of the variants of the "short" allele ("s"), particularly the homozygotes "s/s", were found to be more vulnerable to the negative effects of stress on mood.[8] This observation led to a large series of later studies, which make this polymorphism probably the most extensively examined one in psychiatry.

Since the life trajectory of a patient after having received a cancer diagnosis is characterized by a constellation of stressful life events,

and depression and difficulties in the mental adaptation to cancer occur at various degrees in cancer patients, we decided to examine the role of 5-HTTLPR in oncology.

A first investigation in women with mammary carcinoma considered the effects of stressful life events experienced before cancer diagnosis. A positive correlation had previously been found between the stress score and the size of the tumor at surgery.[9] In the current study on 5-HTTLPR, stress scores were positively and significantly correlated with HAD-D, whereas the polymorphism did not have any significant role on depression.[10]

When MAC-HH and HAD-D were subsequently considered in relation to 5-HTTLPR in women with early breast cancer, the correlation was significant only in the carriers of the "l/l" variant: For patients with advanced cancer the correlation was not dependent on the genotypic variants.[7] The MAC and HADS scores were then analyzed in terms of their change from baseline at diagnosis to the follow-up 1 and 3 months later. MAC-AP displayed a significant spontaneous decrease at follow-up; when the patients were stratified for 5-HTTLPR genotype, the reduction was significant only for the carriers of the "l/l" variant.[11]

Conclusions. These data indicate that when 5-HTTLPR is considered in cancer patients, the presence of the "s" allele is associated with increased difficulties of the mental adaptation to the disease. This finding is in agreement with the most recent reviews and meta-analysis which provide strong evidence for an association between the "s" allele and increased sensitivity to stress and depression in non-oncological patients.[12] Our findings might help to identify the patients with greater difficulties in mental adaptation to cancer, and to guide the appropriate choice for their drug treatment (antidepressants vs anxiolytics).

IV. PHARMACOGENETICS

The serotonin transporter is the molecular target for the action of SSRI antidepressant drugs (AD), and it has been consequently investigated for its possible involvement in the therapeutic response and incidence of adverse effects for SSRIs. Several meta-analyses are available, clearly showing that the "l" allele and the "l/l" genotype are associated with a better clinical response, particularly in Caucasians.[13] We therefore examined in patients with advanced cancers the effects of SSRIs in relation to 5-HTTLPR. The effects of sertraline were sig-

nificant on all the areas considered by MAC and HADS; when the patients were stratified for 5-HTTLPR, the significance was limited to the "l/l" genotype for HAD-A, MAC-HH, and MAC-FS.[14] Citalopram caused a significant reduction of HAD-D and HAD-A; the reduction of HAD-D was limited to the patients carrying the "l/l" genotype.[15]

Conclusions. The effects of SSRIs are not limited to depression, and depend on the 5-HHTLPR genotype of the patients, providing indications for appropriate personalized choice of the drug treatment (SSRI vs atypical non-SSRI AD).

V. GENERAL CONCLUSIONS

(a) Before tumor diagnosis, stressful life events experienced by women with breast cancer are associated with the later development of depressive conditions; 5-HTTLPR does not play any significant role.
(b) After tumor diagnosis, mental adaptation to cancer is characterized in women with early breast cancer by anxious preoccupation which spontaneously decreases at follow-up; the reduction is significant only in the carriers of the "l/l" 5-HTTLPR genotype.
(c) ADs do not act only on depression, and the response is genotype dependent.
(d) 5-HTTLPR has a (limited) role in psycho-oncology, permitting the identification of patients with greater need of support (carriers of "s/s" genotype), and in the case of drug treatment allowing the personalized choice of the drug (benzodiazepines for treating anxiety, or non-SSRI ADs for treating depression in "s/s" patients).
(e) These data are in agreement with the more recent non-oncological reviews, showing a real, though small, effect of 5-HTTLPR on environmental adversity and the action of SSRI ADs.[16]

VI. LIMITATIONS OF THE STUDIES REPORTED

(a) Publication of some articles in journals of limited impact;
(b) Small size of the samples of patients examined;
(c) Size of the contribution of 5-HTTLPR to mental suffering and effects of SSRI in oncology is limited, as in non-oncological patients;

(d) Evidence is accumulating showing serious limitations of the general efficacy of SSRI AD.

VII. ARE SSRI CLINICALLY EFFECTIVE, AND WHAT CAN 5-HTTLPR TEACH US ABOUT THEIR EFFICACY?

Kirsch and colleagues, examining the efficacy of SSRIs from published clinical trials, found that their effects are largely coincident with a placebo effect.[17] A subsequent analysis by Kirsch of the U.S. FDA data which were used for licensing the SSRIs, showed that for mild or moderate depression, the effects of SSRIs were identical to those of placebo;[18] a similar conclusion was the results of a meta-analysis made by Fournier and collagues in 2010.[19] The weaknesses of the process of licensing AD drugs by regulatory agencies is also indicated by the case of reboxetine, which a systematic review and meta-analysis of published and unpublished data showed to be an ineffective and potentially harmful antidepressant.[20]

The question then arises about how these negative data can be reconciled with the pharmacogenetic evidence published for SSRI. In this connection, it is interesting to note that the magnitude of the placebo effect was shown to depend on the functional genetic polymorphism of serotonin-related genes, such as 5-HTTLPR,[21] the G-703T polymorphism in the tryptophan hydroxylase (TPH2) gene promoter,[21] and val158met in catechol-O-methyltransferase.[22]

Moreover, other contradictions still persist, which are commented upon below. The monoaminergic theory of depression and antidepressants is based on the idea that antidepressants inhibit the synaptic reuptake of monoamines, correcting a reduced availability concomitant with depression; agents reducing synaptic availability of monoamines correspondingly induce mood depressive disorders.

When 5-HTTLPR is considered, the carriers of the 5-HTTLPR s/s variant have a less functional 5-HT transporter and a consequent *higher synaptic availabilty of 5-HT (same condition supposed to be obtained after SSRI treatment)*, but at the same time are *more vulnerable* to stressful life events and *less responsive to SSRIs*. Although a limited contribution of 5-HTTLPR to depression and AD drug action is likely to occur,[16] other genes are related to depression and the antidepressant response to SSRIs is involved, for example, cytochrome P450, P-glycoprotein, TPH, COMT, MAO-A, SERT, NET, DAT, 5-HT1A, 5-HT2A, BETA-Adr, and DA, together with signal transduction, stress hormones, circadian rhythm, and NBDF.[23]

The complexity of the neurotransmitter network, together with the similar complexity of the pharmacokinetics and pharmacodynamics of AD drugs is therefore evident, and has to be considered together with the same definition and diagnosis of depression. The depressive mood disorders are progressively shifting away from the psychopathological endogenous vital (melancholic) depression, to include mild reactive presumably nonpathological conditions, with a threshold for clinical response in clinical trials of ADs of marginal clinical relevance.[24] In the case of cancer, the same diagnosis of depression would need to be based on criteria which exclude symptoms and signs caused by the neoplastic disease, such as appetite and weight change, sleep disturbances, and fatigue. For depression in cancer patients, exclusive criteria have been defined, and an in vitro test based on serotonin-induced calcium mobilization in the blood platelets of patients has been developed.[25]

VIII. PERSPECTIVES AND FUTURE RESEARCH

There is an increasing medicalization of mental conditions, leading to a parallel increase in the prescription of neuropsychiatric drugs, contrasted by a lack of new molecular entities: This occurs also for numerous other nonpathological conditions outside psychiatry.

From a pharmacological perspective, there is a lack in the identification of new "ideal" molecular targets against which new agents could be developed, with the following considerations and possible subjects of research:

(a) The condition being treated should be a real "unmet medical need" and not a physiological condition marketed to become a disease;
(b) The target should be in a linear causal relationship with its therapeutic effect;
(c) Problems exist for the translation of the experimental data to the clinical setting, particularly for biotechnological compounds acting on complex networks of effectors; clinical effects are not related to the in vitro evidence, and nonlinear dose-effect relationship are common;
(d) The clinical trials require an open access to the data obtained, with clear thresholds for clinical efficacy and adverse effects;
(e) Role of the ethical committees (review boards) in authorizing clinical trials leading to later licensing of sufficiently innovative new drugs with significant efficacy against real unmet medical needs;

(f) More emphasis on nonprofit basic research against industrially based current approaches.

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