Some Theoretical Considerations on Chalones and the Treatment of Cancer: A Review

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SUMMARY

Growth-inhibitory substances called “chalones” have recently been found in the epidermis and in some other tissues. Recently, the use of such substances in the treatment of cancer has been suggested on the basis of experiments with transplanted tumors and small pieces of such tumors in vitro. It seems well documented that some tumors contain chalone-like substances and that the rate of proliferation in some tumors can be influenced by the tissue-specific chalone. However, from the present knowledge of chalones it seems unlikely that they can be used in cancer therapy. The reported acute necroses in some transplantable tumors (melanomas and chloromas) induced by extracts of normal tissues or of tumors are probably not due to a chalone effect proper (i.e., physiological growth regulation), but to some other mechanism mediated through the vascular bed.

INTRODUCTION

During the last few years, it has been found that the rate of cell proliferation is, in some tissues at least, controlled by specific mitotic inhibitors called chalones. Experiments have shown that chalones are substances that inhibit mitosis and DNA synthesis. Their action seems to be reversible. They act both in vivo and in vitro. Their action is tissue specific, but not species specific. Some chalones seem to require the stress hormones as cofactors (for a recent review, see Ref. 21). A chalone has been defined by Bullough (5) as “an internal secretion produced by a tissue for the purpose of controlling the mitotic activity of the cells of that same tissue.” This definition must be regarded as theoretical. The assay systems used to judge a chalone effect cannot tell whether the factor is an “internal secretion” or whether it is there “for the purpose of mitotic inhibition.” We do not know whether the factor is intracellular or extracellular before extraction. The test systems can tell only whether a certain factor inhibits proliferation alone or in combination with other factors like adrenaline.

Recently, a series of papers (8–11, 23, 26–30) describing the mitosis-inhibiting and necrotizing effect of certain tissue extracts on 4 malignant transplantable tumors (the V × 2 epithelial tumor, a chloroleukemia, and 2 melanomas) have been published. These results have been interpreted as being due to a chalone effect. In the papers mentioned, attention has been drawn to the possibility of using chalones in the treatment of cancer, with phrases such as the following: “the question now obviously arises whether such chalones may be of practical value in cancer chemotherapy to arrest or even reverse tumour growth” (8). “Again it is possible that tumour growth in vivo may be prevented or even reversed by repeated injections of either normal or tumour tissue extracts” (9). “This suggests the possibility of suppressing neoplastic growth by repeated chalone injections” (23). “This fact may prove to have considerable value in that it may provide the basis for the treatment of malignant tumours by chalone containing extracts . . .” (28).

The treatment of malignant tumors with tissue extracts from normal tissues or from tumors has been tried many times in the past. All attempts (thymus extracts, tumor extracts, etc.) in humans have failed, although some growth inhibition has been observed in tissue culture and on transplantable experimental tumors in animals. Because of this, extreme caution is indicated when making forecasts within this area. The statements mentioned, expressing optimistic views regarding the treatment of cancer based on results from tissue culture and experimental transplantable tumors, have already given rise to unrealistic hopes among cancer patients. They have also led to comments in different journals, such as a well-balanced leading article in The Lancet (12), a more optimistic one in World Medicine (24), and even newspaper reports (14).

As a pathologist who has worked with the epidermal chalone for many years, I feel that a word of caution must be raised about optimistic speculations regarding the usefulness of chalones in the treatment of cancer. The evidence for such hopeful suggestions is not convincing. From theoretical considerations, it seems unlikely that chalones can be effective in the control of spontaneous tumors, even if chalones may be of great significance in carcinogenesis.

TUMOR GROWTH IN RELATION TO TREATMENT

Higher organisms contain numerous complicated regulatory mechanisms from the molecular level up to
the total organization of the individual. It is, therefore, also reasonable to assume that the control of growth and differentiation is mediated through feedback systems consisting both of stimulatory, inhibitory, and modulating signals that determine the growth rate, the rate of differentiation, and the rate of cell loss in different organs. From this point of view, carcinogenesis must also involve some damage or destruction of these physiological growth regulation systems, either by virtue of the fact that cancer cells have lost their ability to respond normally to the growth regulation or that there is some error in the system itself, for instance, in the production or the transfer of the signals (for a more extensive review of this problem, see Ref. 20). However, the changes in the growth-regulating system may well be only secondary, and occur as a result of the malignant transformation. When it is said that a disruption of the normal homeostatic balance between cell gain and cell loss is "the basic event in carcinogenesis," and "that this must depend on some change in the control mechanism of which the chalone forms a part," there is no conclusive evidence on which to base such statements.

Tumors are not always characterized by a rapid rate of cell proliferation; in fact, many tumor cell populations have a lower rate of proliferation than that of the tissue of origin (4, 15, 22). The capacity of infiltration, destructive growth, and formation of metastases is probably the most important property of cancer, and the rationale for using pure growth inhibitors for cancer treatment is thus not very obvious, but must rest on the assumption of a higher sensitivity of cancer cells to such agents (2). X-rays, cytostatic agents, and hormones are used in cancer therapy because it is assumed that tumor cells are more sensitive than normal cells or because at least X-rays can easily be topically applied, although not without damage to normal cells. It seems probable that a therapeutic attack only on the proliferation will be a failure, as demonstrated by the very limited effect of cytostatic agents. Good temporary effects with reduction of tumor size seem to be obtained only in those tumors that have a rapid rate of spontaneous cell loss and a short generation time of the cells in the proliferative pool (2). Permanent cure has been reported only in cases in which other forces are most probably also operating. As examples, one may mention the Burkitt tumor with a very high rate of spontaneous cell loss (13) or the chorion-epithelioma, which must be regarded as a transplanted tumor with its peculiar tumor-host relationship.

Accepting that a malignant tumor is not static, but is in a dynamic equilibrium, it is reasonable to think that some growth-regulating forces are still operating in most cases, except possibly in a few of the very undifferentiated and rapidly growing tumors. We know that many hormone-dependent tumors may remain long in the dependent state; for instance, they do not grow without the milieu being conditioned by continuous hormonal influences. We must also remember the well-documented cases of quiescent periods in the development of some tumors, and also the few, but obviously well-documented, cases of complete spontaneous regressions (16). Such observations point to the fact that most tumors are not absolutely unresponsive to host factors, be these of immunological, hormonal, or chalone nature. Most malignant tumors, however, grow and kill the patient in spite of these regulating forces. If the tumor cells are less responsive (in the broadest sense), and the normal cells of the same series retain their normal sensitivity to the controlling signals, then the use of the physiological controlling signals for cancer chemotherapy will theoretically stop the proliferation of the normal cells of that series before they stop proliferation of the malignant cells. That this in fact happens is demonstrated in 2 of the published reports in which the authors say, "It has been established, however, that repeated injections of apparently excessive amounts of chalone are potentially dangerous in that they cause severe suppression of normal granulocyte production..." (29), and "...normal BM [bone marrow] cells are significantly more sensitive to the chalones than are the CHL [chloroleukemia] cells" (28).

The only possible beneficial effects of chalones would occur if the mechanism of action is much more complicated than just inhibition of proliferation, or if it were possible to concentrate the chalone selectivity in the tumor cells (and at present there is no evidence that this could be done), or if the normal cells can survive a prolonged block of DNA synthesis and mitosis, which the tumor cells cannot survive.

TRANSPANTABLE TUMORS TREATED WITH CHALONES

As far as published reports are concerned, all experiments have been performed with transplanted tumors. It is generally accepted that the tumor-host relationship in such instances is very different from the tumor-host relationship in tumors primarily induced by viruses, irradiation, or chemical carcinogens, or occurring "spontaneously" in an animal or human being. "Grafted tumors are not identical with spontaneous tumors, not even in isologous strains. The differential is greatest between natural and transplanted tumors, including those bearing historical names.... In the course of animal passages in alien hosts tumors become more and more degraded, their genetic and antigenic properties become altered, and they may lose their morphologic identity" (17). The rate of cell division in transplanted tumors is generally much higher than in spontaneous tumors.

Some of the experiments reported are from organ or tissue cultures which are known to be very sensitive to growth-inhibitory substances from animal tissues. A great many natural substances extracted from tissues have been shown to exert growth promotion or growth-inhibitory action on cells in vitro. In 1965, Parshley (25) reported the inhibitory effects on growth of a series of tumors in vitro of extracts from adult connective tissue, and it seemed as if the extracts were particularly
effective against sarcomas. In a recent systematic investigation of the presence of growth-inhibitory substances in animal tissues, Bardoz et al. (3) tested more than 1000 fractions of extracts from 28 different bovine or porcine tissues. Antitumor activity was found in 14 fractions from different tissues. Cell culture cytotoxicity was found in 8 fractions from the liver, 1 from the lung, and 2 from the pineal gland.

The tissue specificity, which should be characteristic for chalone effects, is not an easy problem to handle. The starting material for all the epidermal chalone preparations used up until now contains, in addition to keratinocytes, melanocytes, and Langerhans' cells, cells from sebaceous glands, hair follicles, connective tissue, endothelium, blood cells, and nerves. It seems that epidermal chalone is specific for squamous cell epithelium, or that such epithelium is very sensitive to a factor present only in skin extracts. Such specificity is the reason why the V x 2 tumor was selected as test object (11), since it was originally a virus-induced skin tumor which has been serially transplanted for 30 years. It is now very poorly differentiated; no desmosomes and horny pearls are seen. It was said that this tumor arose from the surface epithelium, and that the hair follicles were not involved. This is a very difficult matter to be sure about, but it is used as an argument for the specificity of the epidermal chalone, since "...the hair follicles, from which so many so-called epidermal tumours are derived, have a separate mitotic control system" (11). However, it is obvious that, since the chalone prepared from pig skin had a starting material containing hair follicles, this preparation must also contain a hair follicle chalone (if this exists), and thus the argument of epidermal specificity is not very strong.

However, with the above reservations, it seems well documented in the reports mentioned that the V x 2 tumor, the transplantable melanomas, and the chloromas contain chalone-like substances, and that the proliferative activity in these tumors can be influenced by extracts of the tissue of origin or by extracts of the same tumor. This may be a chalone effect.

POSSIBLE EXPLANATIONS OF THE TUMOR REgressIONS

The reports on regressions and cures of melanomas (23) and chloromas (30) are very interesting indeed. These tumors regress during treatment in a few days, with heavy necrosis and ulceration. A primary immunological reaction can be discarded because of the rapid reaction. However, it seems highly unlikely and unbiological that a physiological growth-regulating substance given in excess to the whole organism should provoke only in the tumor a rapid necrosis, which is due only to growth inhibition of tissue-specific nature. It seems more likely that the extensive necrosis in the tumor is not due to growth inhibition, but is mediated through the vascular bed, possibly as a local Shwartzman's reaction. The preparation phase might be brought about by the inflammatory reaction around the "foreign" transplanted tumor. It is well known that widely diverse agents can be active as the provoking factor for Shwartzman's reaction. Contaminating bacterial toxins might, for instance, be present in the tissue extracts, especially from tumors. A secondary immunological mechanism related to the Arthus' type reaction must also be ruled out, at least in the cases in which tumor extracts were used.

Some reservations regarding the reproducibility of the results have been taken in 1 of the papers (23). It must also be kept in mind that regression of transplanted melanomas is also seen, for instance, after treatment with cortisone alone (1).

The phenomenon of acute necrosis induced by tissue extracts in transplantable tumors is not new. In 1954, Horava (19) described hemorrhagic necrosis in a Walker 256 tumor induced by injection of a fluid obtained from the same tumor. As tentative explanations of this phenomenon, Horava put forward the following possibilities, viz.: substances originating in the tumor itself; host responses, both local and systemic; and causes unrelated to cancer, such as bacterial toxins.

There is, however, at least 1 possible mechanism that might explain the beneficial results described by using chalones on these tumors. As shown by Hempel (18), the Harding-Passey melanoma is a tumor characterized by a rapid turnover of cells. By the labeled mitosis technique, this author showed that the generation time of this tumor is only 26 hr, and the growth fraction is 50 to 70% of all melanocytes present. This means that the lifetime of a tumor cell is very short, in the order of 1 to 2 days. If these tumors are also antigenic, and if a high amount of chalone can for a short time retard the proliferation and enhance the maturation, then the tumor growth could be arrested and the immunological forces of the organism become free to destroy the few surviving malignant cells. This is a theoretical, but real, possibility. Very few tumors, however, have such a rapid turnover rate of the cells. These tumors are probably the very same that are sensitive to cytostatic treatments. Thus chalone treatment would not be more fruitful than cytostatic treatment. An advantage of chalone treatment could be that chalones may not destroy the reticuloendothelial system, as do most of the cytostatic drugs.

CONCLUSIONS

The question of chalones is very important in biology, but, since we do not yet know the normal biochemistry and physiology or the chemical constitution of the chalones, it seems much too early to make optimistic statements about the relationship between chalones and the treatment of cancer. Every effort should be directed toward the possible discovery of the chemical constitution of chalones and the mechanism of action at the cellular and molecular level. It is possible that chalones may be very relevant to the cancer problem, primarily
or secondarily. We do not know at present, and only when it is possible to purify and characterize chalones and to measure their concentration in tissues will we be in a position to study their significance, if any, and their importance for cancer development.

Bullough in recent papers concludes this about the experiments with skin extracts and transplantable melanomas: “Exciting as this discovery may be, it is essential to discourage any great mood of optimism.” “It still remains to be established that the tissue chalones . . . have a role to play in the treatment of cancer” (7). This has long been my opinion.

It seems well documented, and it is biologically reasonable to accept, that differentiated malignant tumors produce the specific chalone of the tissue of origin, and that the rate of proliferation in such tumors can be influenced by the chalones. However, this does not automatically imply that the chalones can be used in cancer therapy. On the contrary, theoretical considerations on the nature of chalones make it doubtful or impossible to believe that such substances can be used to cure cancer.

REFERENCES

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