

EDITORIAL

## Steroid Hormones are Produced at the Sites of Action

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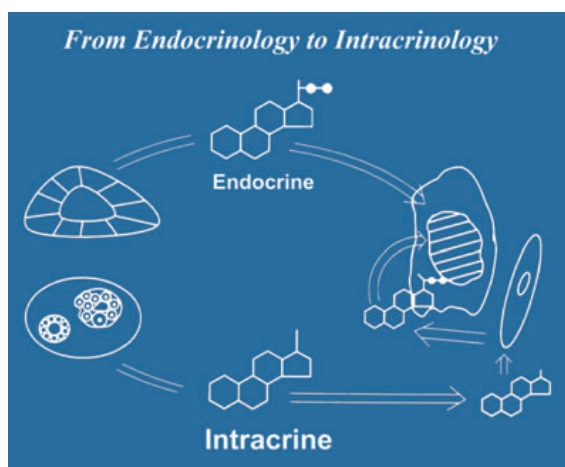
### Classical concept of steroid hormones

Steroids are synthesized in endocrine organs, such as adrenal glands, ovaries and testes, and secreted into the circulation where they exert their effects on target tissues in which specific receptors are located. Along with this concept, hormonal actions of steroids have been in general considered to be determined by the following three factors: 1. the amount of hormones produced in these endocrine organs; 2. the amount of hormones, especially free ones, present in the circulation; and 3. the presence or absence of specific receptor(s) in the target tissues and if present, how abundant are receptors expressed in these target tissues? This concept is illustrated in the upper portion of Figure 1, which corresponds to so-called classical endocrinology of steroids. Numerous attempts have been made toward precise measurement of serum or plasma concentrations of active or free forms of steroids, assessment of the capacity of hormonal synthesis using stim-

ulation tests or other methods, and precise evaluation of the status of specific receptors in target organs in order to understand both the physiological and pathological conditions of steroid hormone action based on this classical concept. This field of medicine has been generally defined as “Endocrinology”.

### Steroid hormone action beyond classical concept: An example of estrogen-dependent breast cancer in postmenopausal women

Estrogen-dependent breast cancer is breast cancer in which the estrogen receptor (ER) is expressed in carcinoma cells, and estrogen plays pivotal roles in its pathogenesis and development. This type of breast cancer is obviously one of the so-called endocrine diseases. However, ER-positive breast cancer frequently occurs in postmenopausal women or men, in which the serum or circulating levels of estrogen are markedly low. Therefore, along the lines of the classical concept described above, numerous attempts have also been made to demonstrate evidence of increased levels of circulating estrogen or to identify “bad estrogen,” such as its metabolized forms, to account for the development of ER-positive breast cancer in these patients. However, almost all attempts have failed to detect increased levels of circulating estrogen compared to age-matched controls or estrogen specific to the serum of breast cancer patients. These findings even cast doubt upon the significance of ER in carcinoma cells in the biological features of these types of human breast cancer.



**Fig.** Schematic illustration of summary of “Endocrinology” and “Intracrinology”

### Development of the concept of Intracrinology

There are no significant differences in serum estrogen status between patients with breast cancer and their age-matched controls but various studies from

the early 1980s demonstrated increased tissue estrogen concentrations in the great majority of postmenopausal breast cancer despite its markedly suppressed serum levels. The estrogen concentrations of breast cancer tissues were subsequently found to be higher than those of benign disorders, such as fibroadenoma or even other portions of the body in the same patients. Subsequent analyses demonstrated that breast cancer in postmenopausal women actively transformed weak adrenal androgens such as DHEA or androstenedione, which is still abundantly present in the circulation of these patients, into estrogen *in situ* through overexpression of the enzymes involved in local estrogen biosynthesis, especially aromatase. This locally-produced estrogen works on the ER present in carcinoma cells, which made it possible for ER-dependent carcinoma to proliferate in the first place despite markedly low levels of circulating estrogen which represent a rather hostile environment for cancer development. This mode of hormonal action in breast cancer, where hormones produced locally at the sites of their actions work on receptor-positive cells, as also revealed by other works demonstrating *in situ* biosynthesis of dehydrotestosterone in human prostate cancer patients, has led to the concept of "Intracrinology" summarized in Figure 1. In this concept, an important factor to determine is how biologically-active hormones are pro-

duced at the sites of their actions. Numerous attempts have been directed toward the analysis of hormone production at target sites and one of the major clinical achievements based on this concept of Intracrinology is the development of aromatase inhibitors which markedly reduce intratumoral estrogen production and is currently established as the gold standard of endocrine therapy for hormone-dependent postmenopausal breast carcinoma patients.

### **Future perspectives**

This concept of Intracrinology applies not only to sex steroid-dependent malignancies, such as breast, prostate, and endometrial cancer, but also to almost all phenomena in which sex steroids are involved, such as osteoporosis, atherosclerosis, and various abnormalities of the central nervous system associated with decreased serum estrogen or androgen concentrations. In addition, this concept is also applicable to glucocorticoids or mineralocorticoids and is considered to play important roles in obesity or other features in which these hormones are involved. Therefore, an application of this concept may shed new light on the pathogenesis and/or development of these disorders. In addition, various modulators of this *in situ* steroid metabolism are presently being developed as therapeutic agents.