Review

Melatonin Study, Classic and Modern

By Wataru MORI, M. J. A.*)

(Communicated Dec. 12, 1996)

Abstract : It has been experimentally verified that melatonin has various biological functions of much interest, but the today's trend harboring an idea that melatonin is likely to be a cure-all is extreme by any stretch of the imagination. What should be now sought will be to take a short rest from experiments and to arrange a huge number of experimental data so far obtained as well as to judge calmly the real state of things. I have had a very happy experience in extending melatonin study from so-called classic to modern parts of it. But the problem of it, which all the time had something been on my mind was that no theoretical linkage was likely to be gained between a classic part of the experiment, that is, more lightening of amphibian skin colors and a modern part, that is, its influence on mammalian lipids or immune systems. An idea occurred to me, as far as my research results are concerned, that the major part of such a linkage between both can be put in order by understanding that the feature of melatonin is a direct or an indirect functions of the anti-ACTH · glucocorticoid system. And probably, this way of thinking helps arrange many other results of melatonin research.

Key words : ACTH; glucocorticoid; melatonin; pineal gland.

No matter what not a few well-informed persons warn of, melatonin seems to have been permeating among the people very forcibly in the United States of America, and now coming to Japan.

In 1956 I happened to get a chance to study at Yale University School of Medicine, U. S. A., and there luckily had joined the research team that later discovered melatonin in the laboratory of Prof. Aaron B. Lerner.[1),2)] I had originally specialized in pathomorphology, but I was chosen and introduced to this laboratory by Prof. Shigeo Okinaka for one of the reasons he told me, that is: special improvements in bioassay using frog skins, i.e. their pigment cells, were urgently required in Lerner's laboratory, and for this purpose such staff as I who could identify the morphology of cells were needed. At that time the hormone that deepens the skin color of frogs, i.e. diffuses melanin granules in the skin melanocytes was already known as an extremely important substance in the pigment-biological research. This is the melanocyte stimulating hormone (MSH), which is derived from the hypophysis. Then, what Lerner's group had been pursuing desperately was a new hormone that would agglutinate melanin granules around the nuclei antagonistically against it. It was anticipated with rather certainty on the basis of the literatures or the results of preliminary experiments that this new hormone was likely to be present in the pineal body.

My main work in this laboratory was to carry out a bioassay as precisely as possible and to assist in isolation of the hormone, to which the biochemists were devoting their daily efforts using bovine pineal bodies as a raw material. As it is mentioned in a research paper[3)] that "The bioassay procedure used in the isolation work (of melatonin) is reported here." I combined a microscope with a photometer to develop the device for much more precise bioassay than before, and assayed the blind samples brought one after another by making the most of the device, leading to the successful isolation of the targeted pineal hormone. This new substance called melatonin truly splendidly lightened the skin color of frogs antagonistically against MSH. But attempts to whiten the human skin color or to inhibit growth of the experimental melanoma ended in an unexpected, negative result. These are

*) Present address: c/o The Japanese Association of Medical Sciences, 2-28-16 Honkomagome, Bunkyo-ku, Tokyo 113, Japan.

the so-called classic part of the melatonin study, carried out mainly in the late 1950s.

The so-called modern study on melatonin thereafter performed, tended to rather widely disperse from Lerner's laboratory to various places in the world; many of these have blossomed after the years 1970s. I myself returned to Japan in 1959 and became again a morbid anatomist, being loaded with a heavy daily task. But while continuing pathoanatomical work in such circumstances I have somehow come to think that melatonin may be one of stress hormones and be antagonistic against glucocorticoid. In an actual research paper[4] these particulars are given like this: ". . . various experimental studies and considerations, including experience in human pathology, have led us to hypothesize that melatonin might be an effective antagonist against adrenocortical hormone, glucocorticoid."

On one hand there was quantifiable clear pathoanatomical knowledge indicating that there existed negative correlation between thickness of an adrenal cortex and weight of a pineal body.[5] But the main basis for it seemed to be attributed to rather the intuition or animal sensation created spontaneously by having repeated observations of various viscera during the pathoanatomical operation, autopsy.

Thereafter, some more animal experiments have been performed in such a direction to reveal that melatonin is evidently antagonistic to glucocorticoid.[4,others] Definitely speaking, the changes in the thymus, lymph nodes, pancreatic Langerhans' islets, and blood lipids, caused by dosage of glucocorticoid are deterred or reduced by dosage of melatonin. The suppression effect of melatonin on hyperlipemia, sequentially confirmed, can be explained to be one of the functions of anti-glucocorticoid.[6,others] And these surely constitute links in the modern part of melatonin study. In this sense, more luckily I can probably say that I could myself experience both classic and modern studies on melatonin.

But it weighed upon my mind that there seemed to be no linkage among the following things: such two classic and modern studies, in terms of phenomena lightening of the skin color of frogs and suppression of atrophy in the thymus or lymphatic tissues of mice, etc., and moreover in other words anti-MSH and anti-glucocorticoid. Generally speaking, it does not matter what the origin or conception of the research is, even if it is accidental, logical or revelational. Nevertheless, once visualized outcomes have come out one after another and appeared before my eyes, I desire to create the systematic logic governing all of these, and, if possible, to have the theory which can explain all in the same principle; this is my way of thinking as a pathologist. Along this line I hope to find out some theoretical linkage between two clearly distinct study results I have obtained on melatonin.

As mentioned at the beginning, basically I am a pathomorphologist but know little about biochemistry. Even when I deal with a substance I give attention to its influence on tissues or cells as well as to changes in these caused by the substance, but I was rather indifferent to the structure of the substance itself or its chemical formula. Thus, when I think over the relation between these two groups of the studies, it can not be denied that there was always a general pathomorphological idea involved chiefly in my way of thinking. But if the starting point of consideration is on the chemical structure of a substance, I am not sure what will happen to me.

In fact, it was already reported more than 40 years ago that a considerable part of the structure of MSH which has spurred researchers into discovery of melatonin was occupied by corticotropin-A itself. Also the corticotropin-A, i.e. ACTH itself was known to have a function of deepening the skin color of frogs. It follows from the foregoing that the function of melatonin which has been only considered to be anti-MSH ought to actually have been anti-ACTH as well. Moreover, if I give full play to my imagination, anti-ACTH itself may be the true form and anti-MSH may be its derivative. No further explanation is needed of the relation between ACTH and glucocorticoid, and in this way of thinking anti-MSH and anti-glucocorticoid, i.e. the two above-mentioned studies can be easily connected with each other through the medium of ACTH. And with this intention, many research results until today produced by other researchers can probably be put in order to some extent.

As far as melanocytes in frog skins are concerned, the antagonism between MSH and melatonin can be observed not only *in vivo* but *in vitro* and thus both of them may be no doubt considered to be endocrinologically at an identical level. But all the experiments so far undertaken on the antiglucocorticoid function of melatonin were done *in vivo*; since these results were produced through black boxes of living bodies, there are still many uncertain points in the interrelation between these two hormones. Is melatonin involved in any direct antagonism against

glucocorticoid ? or through ACTH ? Even the possibility that anything may exist for melatonin like glucocorticoid for ACTH can be hardly denied.

Along with enormous numbers of the research papers published on the function of melatonin, today melatonin is so overestimated in a part of the society that the people are much confused by enthusiastic information. Even with the melatonin's function on circadian rhythm, which is now most widely accepted and believed to be the reason why it can be used as a sleeping drug, true mechanism is not clarified completely yet. So-called melatonin effect could only be a result, and not a driving force, of such a rhythm in human being. Realizing its reality, others as well as myself may think that certain calm measures should be taken against this situation. Although there are still many animal and human cases which should be examined, it may be also important to take a rest for a while from the work to think calmly about this.

Is it advisable under these circumstances that as such an attempt, all melatonin effects, either direct or indirect, be put in order from a standpoint of the anti-ACTH · glucocorticoid system ? In this way, the majority of the so-called melatonin effects may be able to be arranged and so it might lead to discovery of new potential effects of glucocorticoid, which have never been detected as yet. Assuming that under this idea the feature of melatonin effects will be considerably theorized in the future, the present state of the confusion is more likely to be even natural in a sense, because there are now still not a few uncertain points even in the feature and function of glucocorticoid itself.

Thus, I visualize one hypothesis in my mind. To begin with, melatonin might be present inside living bodies as substances or a substance with functions against the ACTH-glucocorticoid system. In an actual research process for solving the mystery, its function that is antagonistic against MSH to be called the glucocorticoid-related substance was first discovered, and then the function of antagonism against glucocorticoid itself was realized. So to speak, its resolution proceeded rather in reverse, as if means had been confused with ends. And if it is really true, what should be attempted in the future may be to ascertain academically which part of the ACTH-glucocorticoid system melatonin is antagonistic to. Thus, if both classic and modern studies on melatonin become linked with each other with very reasonable continuity and consistency, naturally I will feel myself greatly relieved at them.

References

1) Lerner, A. B., Case, J. D., Takahashi, Y., Lee, T. H., and Mori, W. (1958) J. Amer. Chem. Soc. **80**, 2587.
2) Lerner, A. B., Case, J. D., Mori, W., and Wright, M. R. (1959) Nature **183**, 1821–1822.
3) Mori, W., and Lerner, A. B. (1960) Endocrinology **67**, 443–450.
4) Mori, W., Aoyama, H., and Mori, N. (1984) Jpn. J. Exp. Med. **54**, 255–261.
5) Hasegawa, A., and Mori, W. (1980) Acta Pathol. Jpn. **30**, 407–410.
6) Aoyama, H., Mori, N., and Mori, W. (1988) Atherosclerosis **69**, 269–272.