ESSAYS ON APS CLASSIC PAPERS |

Adrenocortical function, feedback, and alphabet soup

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IN THE 1930s, scientists were not wordy. Dwight J. Ingle and Edward C. Kendall published an approximately one-column-long paper (half a page, with data) in Science that concluded: “Our results indicate that the anterior pituitary or some mechanism which controls its activity is sensitive to variation in the amount of cortin in body fluids or to physiologic functions influenced by cortin and that changes in the adrenal are mediated by changes in the output of the adrenotropic principle from the pituitary” (8). Ingle and Kendall (Fig. 1) had previously reported that this might be so through studies of the effects of cortin (adrenocortical extract) on adrenal regeneration. However, Ingle followed up the suggestion provided in the Science paper with an immaculate three-page paper in the American Journal of Physiology that nailed the issue (7).

Typical of Ingle’s work, the four sets of controls for the two experimental groups were both necessary and sufficient to answer the question. The observation was that treatment of rats with cortin resulted in marked adrenal atrophy; the question was whether the treatment was a consequence of a direct effect of cortin on the adrenals or an indirect effect through modulation of ACTH secretion from the anterior pituitary. Ingle chose to answer the question by treating intact and hypophysectomized rats with large daily doses of cortin and to treat a second group of hypophysectomized rats with both an ACTH preparation and cortin, thus testing whether the effects of cortin were direct or indirect. However, hypophysectomized rats eat less and have small adrenals, so Ingle included a pair-fed intact group to test whether reduced feeding decreased adrenal weight (it did not). The paper includes a table of final body weight and a figure showing scattergrams of the six groups of rats studied. The issue was put to bed: cortin caused adrenal atrophy; injection of ACTH in hypophysectomized rats blocked the cortin-induced adrenal atrophy. Therefore, Ingle appropriately concluded that “the hypothesis that atrophy of the adrenal cortex may be due to restriction of the output of the adrenocorticotropic principle of the anterior lobe of the pituitary is supported by these observations” (7), and a cottage industry in trying to understand further the long-loop negative feedback action(s) of glucocorticoids on function of the hypothalamo-pituitary-adrenal (HPA) axis was born.

This cottage industry persists to the present, with many labs throughout the world in hot pursuit of how, and where, glucocorticoids exert their major inhibitory effects on the HPA axis, and the issue is still not resolved. Many suggest that the feedback actions of glucocorticoids on ACTH secretion are on the hippocampus, where there is such a seductively high concentration of receptors (see, e.g., Refs. 4, 6, 11); others suggest that a major site is at the corticotropin-releasing factor (CRF) neurons in the hypothalamus (see, e.g., Refs. 3 and 5), and still others point to the corticotrope in the anterior pituitary as a major site (see, e.g., Refs. 10 and 12). Agreement is yet to come about on the issue so clearly raised by Ingle in the 1930s.

Ingle and Kendall worked closely together at the Mayo Clinic in the 1930s, and it was a very effective collaboration that continued, between the consummate physiologist and the equally consummate chemist. Kendall was responsible for characterization and synthesis of many adrenal steroids, and in 1950 he shared the Nobel Prize in Physiology or Medicine for his work on adrenal steroids with Tadeus Reichstein at the Pharmaceutical Institute in Basel, Switzerland, and with Philip S. Hench, who demonstrated the powerful effects of treating patients with rheumatoid arthritis, as well as a host of other diseases, with synthetic preparations of cortisolone (1). It is because of the work of Kendall and Reichstein that the adrenal...
steroids are frequently referred to as single letters of the alphabet.

The steroids were isolated from adrenal glands by extraction with organic solvents, the extract was concentrated, and then aliquots were spotted on paper or alumina columns for subsequent chromatographic separation in one or another solvent mixture. Because the mixture of steroids in the extract was separated by chromatography into different bands or factions of unknown substances, both Kendall and Reichstein labeled their chromatographic spots with letters. Thus, Kendall’s Compound B was corticosterone, the major glucocorticoid secreted by the rat. Similarly, Reichstein’s Substance S turned out to be 11-deoxycortisol, and Kendall’s Compound E was cortisone (11-dehydrocortisol). Kendall’s Compound F (or Reichstein’s Substance M) was cortisol, the major adrenal glucocorticoid secreted by humans. Both the proper and the familiar names of these adrenal steroids are long, many in the range of 14 letters or so. Therefore, it became common usage to refer to the specific steroid by its chromatographic identification by either Kendall or Reichstein: B, E, F, or S. The clinical (and some basic) literature still uses this shorthand. When an inhibitor of the adrenal enzyme 11β-hydroxylase, such as metyrapone, is used to determine the effects of reduction of negative feedback on ACTH by the active adrenal hormone, it is common to refer to measurement of Compound S (2). Similarly, F is measured in urine (urinary free F) to determine activity in the adrenocortical system. There are letters that have identified enough chromatographic spots to fill the alphabet twice; however, only Compounds B, F, and S are still in some use today. I personally prefer the use of B and F to the other common abbreviation, “cort”, which does not distinguish between the two active adrenal glucocorticoids.

Ingle and Kendall had a long and illustrious interaction. When the chromatographic letters had been distinguished as chemical entities and synthesized, Ingle proceeded to test the relative biological efficacy of many different compounds (e.g., Ref. 9). Ingle’s work provided the impetus to generations of scientists to study negative feedback regulation in endocrine systems and generally showed how clean experiments should be designed.

REFERENCES