Emile Theodor Kocher’s findings in Switzerland in the 1880s that the surgical removal of the entire thyroid gland led to severe physical and intellectual decline in patients made it clear that the thyroid produced a key substance necessary for normal human function. Indeed, this was confirmed by the British physician George Murray in 1891, who first successfully treated a patient with severe hypothyroidism with the sc injection of a sheep thyroid extract. Since these discoveries more than 120 years ago, much has been learned about the actions of thyroid hormones in humans. We now know that the thyroid secretes both T4 and T3 but that available cellular T3 can be exquisitely controlled by a family of deiodinase enzymes that either produce or consume T3. Furthermore, access of T4 and T3 to distinct cell types is mediated by cell surface transporters, the most well-described being the monocarboxylate 8 transporter. Mutations in this transporter in humans lead to a severe X-linked neurological syndrome termed the Allan-Herndon Dudley syndrome. Finally, since the identification of T3 by Pitt-Rivers in 1952, it has become clear that its actions in the nucleus via thyroid hormone receptors and their coregulators mediate the regulation of genomic programs that are key to the role of thyroid hormones systemically. Based on the discoveries over the last 120 years that have led to this understanding of thyroid hormone action, it is only fitting that to celebrate the centennial of The Endocrine Society, we review the impact of two key papers published in *Endocrinology* that led to the modern understanding of thyroid hormone action.

In the 1960s, the work of Tata (1) had established that the administration of T3 led to the increased synthesis of mRNA as a necessary function of its action. Furthermore, thyroid hormone action could be determined in vivo by increased oxygen consumption, increased mitochondrial α-glycerophosphate dehydrogenase, and finally by the inhibition of TSH secretion by the pituitary (2–4). With this context in place, the laboratory of Jack Oppenheimer (Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York) was working to determine how thyroid hormone engaged target tissues. Indeed, at the time this was believed to be a slow process, given the amount of time hormone action took in vivo. However, in 1972 Oppenheimer and his colleagues determined that administered T3 bound to specific high-affinity binding sites in the nucleus, suggesting the existence of receptors for the hormone in rat liver and kidney (5). Thus, a hypothesis was generated whereby these specific binding sites mediated the actions of T3 in tissues in which there was a clear response such as the liver, heart, and kidney, whereas tissues such as the brain that did not respond physiologically in context of oxygen consumption or mitochondrial activation to T3 would not have these sites.

To test this hypothesis, Oppenheimer et al (6) set out to compare the existence of these T3-binding sites in a variety of rat issues that were believed to be either T3 responsive or not. This work, published in *Endocrinology* in 1974, tested the ability of T3 to bind to nuclear sites in the liver, kidney, pituitary, heart, brain, testis, and spleen (6). To accomplish this in vivo in the rat, the investigators first determined, using radioactive T3 (125I-T3), the equilibrium time point by which plasma and the target tissue had equilibrated in context of the administered 125I-T3. Then animals were killed at the equilibrium time point for the target tissue to be tested in the presence of a constant amount of injected 125I-T3 with increasing amounts of nonlabeled T3. After isolation of the nuclei, this methodology allowed for the calculation of the amount of T3...
bound to the nuclear fraction. To the investigators’ surprise, they found that all tissues had nuclear T₃ binding sites, with the pituitary being the greatest followed by the liver and the heart. Tissues previously believed to be unresponsive to T₃ (brain, testis, and spleen) had significant binding, although lower than the liver. Thus, for the first time, these investigators demonstrated that the T₃ response may be different biochemically or physiologically in a target tissue-dependent manner. Most importantly, these critical experiments set the stage for the future identification of nuclear thyroid hormone receptors, the first of which was cloned in 1986 (7, 8). Subsequent work identifying T₃-responsive pathways demonstrated that oxygen consumption and mitochondrial action need not be the only pathways targeted by T₃. Finally, these beautifully crafted experiments showed that in the euthyroid state, not all T₃-binding sites were occupied, paving the way for the notion that the unliganded thyroid receptor could in fact have activity.

Whereas the work of the Oppenheimer laboratory demonstrated distinct nuclear T₃-binding sites in target tissues, Silva and Larsen (the Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts) (9) subsequently showed that in the pituitary the source of this T₃ appeared to be from the direct monodeiodination of T₄ in the local environment. Indeed, the discovery of in vivo peripheral deiodination dated back to the discovery of T₃ by Gross and Pitt-Rivers (10), but significant work by a number of laboratories demonstrated that this could occur in specific tissues. Because a number of groups had detected the direct conversion of T₄ to T₃ in central nervous system tissues, Crantz et al (11) set out to determine whether the T₃ that bound to the nuclear sites in the brain resulted from plasma T₃ or locally generated T₃. To determine this, Crantz et al (11), in their experiments published in *Endocrinology* in 1982, used ¹³¹I-T₃ and ¹²⁵I-T₄ injected in conjunction in rats to determine the source of T₃ bound to nuclear receptor binding sites in the cortex and the cerebellum. Importantly, at all time points examined, the vast majority of the bound nuclear T₃ resulted from the monodeiodination of ¹²⁵I-T₄ rather than circulating plasma ¹³¹I-T₃. In fact, their calculations demonstrated that in the euthyroid state, 94% of thyroid nuclear receptors were bound in the cortex with 73% of the T₃ bound resulting from locally generated T₃. Cerebellar nuclear receptors were 56% occupied in the euthyroid state, with 60% of these sites occupied by locally generated T₃. The studies described in this paper clearly estab-
lished that the local generation of T₃ in target tissues can determine hormone action potentially independently of the circulating or plasma T₃. Indeed, the deiodinase activity that Krantz et al had detected was that of the type 2 deiodinase and knockout of this enzyme in mice leads to a decrease of approximately 50% of neuronal T₃ (12).

Clearly, much remains to be learned in how the thyroid hormone targets unique cell types. It has now become clear that cellular thyroid receptors can mediate nongenomic actions of the hormone. Additionally, unique coregulators modify the T₃ response in a cell-specific fashion. Finally, the deiodinase family can either activate or inactivate T₃ production in a target cell. Still, the discoveries presented here provided key insight into the physiology of thyroid hormone action that are still relevant currently, and this is borne out by the fact that both of these papers are still cited today.

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