CC/NUMBER 41
OCTOBER 10, 1983

This Week's Citation Classic

Gavin J R, III, Roth J, Neville D M, Jr., De Meyts P & Buell D N. Insulin-dependent regulation of insulin receptor concentrations: a direct demonstration in cell culture. *Proc. Nat. Acad. Sci. US* 71:84-8, 1974. [Diabetes Sect., Clin. Endocrinol. Br., Natl. Inst. Arthritis, Metab., and Digestive Dis.; Sect. Biophys. Chem., Lab. Neurochem., Natl. Inst. Mental Health; and Immunol. Br., Natl. Cancer Inst., NIH, Bethesda, MD]

When cultured human lymphoid cells were incubated with native insulin, there was a time, temperature, and hormone concentration-dependent reduction in insulin receptor sites. This study represents a direct demonstration *in vitro* of the ability of a hormone to regulate its homologous receptor concentrations at the cellular level. [The *SCI*® indicates that this paper has been cited in over 770 publications since 1974.]

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July 7, 1983

"The general field of peptide hormone-receptor interactions was still in its infancy when I joined Jesse Roth's lab in early 1971. Nevertheless, receptors were already viewed as rather passive participants in hormone action, while the dynamic regulatory aspects of hormone-mediated biologic responses were attributed entirely to fluctuations in the availability of potent circulating hormone. Our laboratory proposed the unconventional concept that receptors could play a much more direct role in the regulation of hormonal action in health and disease states. The initial data that strongly supported this view were the apparent inverse relationship between insulin binding to hepatic membranes and serum IRI in the insulin-resistant ob/ob mouse.[1] We therefore pursued the hypothesis that this reciprocal relationship between insulin and its receptors in the obese mouse reflected a major and perhaps a general mechanism for hormone-receptor regulatory interactions. This view was neither widely held nor readily embraced in the early 1970s.

"Jesse's laboratory was moving in the direction of developing methods for evaluation of receptors in man when I joined the group. My studies with various components of whole blood led to the description of insulin receptors in red and white blood cells in man. These findings led to the suggestion by David Neville that I screen some of the human lymphoid cell cultures for receptors in order to obtain a more plentiful (and homogeneous) tissue source for receptor characterization studies. Thus began our work with cell line #4265 and its more celebrated counterpart, the IM-9 cell.

"The availability of receptors in cultured cells provided the opportunity to test directly what effects of chronic exposure to insulin *per se* could be demonstrated on receptor binding activity in human cells. With help from Maxine Lesniak, it did not take long to design a series of experiments that could reasonably test the questions of interest to us.

"With our first few experiments we found that, indeed, cells chronically exposed to 10^{-7} M insulin (vs. acute exposure) had a markedly reduced ability to subsequently bind insulin. It was something of a shock when the data were not received well by our weekly data club. A strong sentiment was voiced that all our findings could be explained by contamination with residual insulin or some technical artifact. My only secure allies in the midst of vociferous skeptics were Jesse and Maxine. A series of rigorous control studies eventually quelled the earnest reservations of the data club and dispelled the contamination issue. The findings soon thereafter emerged as the first direct demonstration of regulation of a hormone receptor by its homologous peptide hormone. The concept of dynamic receptor regulation in hormone action was now placed on firm footing. The subsequent demonstration by Roth and Lesniak[2] of highly sensitive and specific regulation of GH receptors by hGH in these same cells was strong confirmation of the presence of this dynamic mechanism. Thus, it is all the more pleasing that from those stormy beginnings we have come to *Citation Classics*.

"I think this work is so frequently cited because it has contributed a great deal toward establishing equal status to the receptor as a key determinant in the dynamic regulation of hormone action. The term 'down-regulation' has been coined out of these observations, and mechanisms for this process have been described in recent literature.[3] While the concept of down-regulation does not account for the entire spectrum of known relationships between circulating hormones and tissue receptors, it has certainly been shown to be a fundamental mechanism with wide applicability, particularly in situations where receptors are chronically exposed to high levels of homologous hormones."

1. **Kahn C R, Neville D M, Jr. & Roth J.** Insulin-receptor interaction in the obese hyperglycemic mouse. *J. Biol. Chem.* 248:244-50, 1973. (Cited 390 times since 1973.)
2. **Lesniak M A & Roth J.** Regulation of receptor concentration by homologous hormone: effect of human growth hormone on its receptor in IM-9 lymphocytes. *J. Biol. Chem.* 251:3720-7, 1976. (Cited 245 times since 1976.)
3. **Hizuka N, Gorden P, Lesniak M A, Van Obberghen E, Carpentier J L & Orci L.** Polypeptide hormone degradation and receptor regulation are coupled to ligand internalization—a direct biochemical and morphologic demonstration. *J. Biol. Chem.* 256:4591-7, 1981.