C-peptide of Insulin

MELISSA EMERY THOMPSON
University of New Mexico, United States

Insulin is a peptide hormone secreted by pancreatic beta cells in response to elevated glucose levels in the bloodstream, such as following food intake. It functions to prevent a hyperglycemic condition by promoting the uptake of glucose by fat, muscle, and liver cells, thereby serving a critical anabolic function and storing energy for later use. Insulin also provides a signal of energy balance to the brain, where, in combination with other metabolic signals, it regulates food intake in service of the long-term maintenance of body fat stores. Insulin also has reproductive effects, upregulating gonadal production of steroid hormones (Poretsky and Kalin 1987). C-peptide is a by-product of insulin synthesis that can be used as a biomarker for metabolic status in primates. During the final conversion of proinsulin to insulin, the connecting peptide ("C"-peptide) is enzymatically cleaved from insulin's A and B polypeptide chains. The C-peptide may itself have direct metabolic effects at the level of the kidney, but it is most often utilized as a proxy for insulin production. Insulin has a very short half-life, and a large and variable fraction is promptly metabolized by the liver before reaching the general circulation. C-peptide is produced on an equimolar basis with insulin yet is not metabolized as quickly, and thus it may be more representative of the rate of insulin production than blood insulin levels (Bonser, Garcia-Webb, and Harrison 1984). C-peptide is also excreted into urine at a consistent rate, making non-invasive testing feasible. C-peptide testing was first developed for diagnosis and monitoring of diabetes, but it has recently been applied for assessing energetic condition in primates (Emery Thompson and Knott 2008).

Primatological field research frequently entails studies of how ecological changes and the availability of energy affect primate health and behavior. Many studies rely on broad-scale environmental measures, such as habitat quality, seasonality, and food availability, as approximations for energetic stress. Increasingly, however, primatologists want to know how individual primates may be affected differently by ecological stress, and how variation in individual condition may affect mate choice, social behavior, reproductive function, and health. Weighing animals or quantifying nutritional intake and energy expenditure are often not feasible, particularly over the long term. This has made non-invasive biomarkers, such as C-peptide, particularly attractive. Primate studies have demonstrated that urinary C-peptide correlates with other indices of energetic condition, such as food availability, dietary quality, daily ranging/activity, calculated energy balance, and weight change.

Measures of energetic condition have the potential to capture various dimensions, such as caloric intake, nutrient sufficiency, and energy expenditure, at different timescales. A challenge for primate energetic studies is to understand how these complex phenomena are reflected in a singular measure, such as C-peptide. The metabolic role of insulin is both instantaneous, as a response to immediate ingestion of carbohydrates and protein, and longer term, as a means to regulate energy stores. Insulin levels immediately following food ingestion may not be representative of overall energetic health. In wild primates, food is usually ingested throughout the day, rather than in "meals," minimizing transient fluctuations. The use of urinary C-peptide also allows assessment of average levels accumulated in urine over a period of hours. However, it is recommended that sample collection be standardized to a particular time of day, such as first morning, or that analyses average across multiple samples.

Several studies of humans and nonhuman primates find positive correlations between body mass change and C-peptide levels, supporting the conclusion that C-peptide is a valid assessment of *energy balance*, or the net difference between caloric intake and expenditure. Available data suggest that C-peptide is not simply a measure of relative caloric intake. For example, the

The International Encyclopedia of Primatology. Edited by Agustín Fuentes.

DOI: 10.1002/9781119179313.wbprim0159

changes in C-peptide that accompanied caloric restriction and the subsequent return to normal diet in macaques were closely correlated with changes in body mass (Girard-Buttoz et al. 2011). Other studies demonstrate that high energetic expenditures, such as during mating effort (Higham, Heistermann, and Maestripieri 2011) and lactation (Emery Thompson, Muller, and Wrangham 2012), can have important influences on C-peptide levels.

As with other hormones, insulin acts via receptors, which can vary in density and sensitivity. In humans and captive primate models, obesity is associated with a relative resistance to insulin. Human pregnancy is also characterized by increasing insulin resistance, facilitating nutrient availability for the fetus. It not well understood how variation in body composition and reproductive status may affect insulin sensitivity in different primate species.

Commercial C-peptide assays are available in both enzyme and radioimmunoassay formats. The assays vary in their sensitivity to detect small amounts of C-peptide, which may be an important consideration for some studies. As antibodies are created to bind human C-peptide, assays may perform less well for other primates. In many cases, increasing the incubation time, even overnight, can improve assay performance by allowing competitive binding to achieve equilibrium. Assays have been used successfully with all four great apes, several cercopithecine species, and a colobine, and there is promising preliminary data from New World species. C-peptide can only be assessed in blood and in urine, creating a challenge for collection from small and/or highly arboreal primates, and from particularly wet or dry habitats.

SEE ALSO: Cortisol and Other Glucocorticoids; Diets and Nutrition; Energetics; Environmental Stress; Health Assessment; Immunoassays

REFERENCES

Bonser, Anne M., Peter Garcia-Webb, and Leonard C. Harrison. 1984. "C-peptide Measurement: Methods and Clinical Utility." *Critical Reviews in Clinical Laboratory Sciences*, 19: 297–352. DOI:10.3109/10408368409165766.

Emery Thompson, Melissa, and Cheryl D. Knott. 2008. "Urinary C-peptide of Insulin as a Non-Invasive Marker of Energy Balance in Wild Orangutans." *Hormones and Behavior*, 53: 526–535. DOI:10.1016/j.yhbeh.2007.12.005.

Emery Thompson, Melissa, Martin N. Muller, and Richard W. Wrangham. 2012. "The Energetics of Lactation and the Return to Fecundity in Wild Chimpanzees." *Behavioral Ecology*, 23: 1234–1241. DOI:10.1093/beheco/ars107.

Girard-Buttoz, Cédric, James P. Higham, Michael Heistermann, Stefan Wedegärtner, Dario Maestripieri, and Antje Engelhardt. 2011. "Urinary C-peptide Measurement as a Marker of Nutritional Status in Macaques." *PLoS ONE*, 6: e18042. DOI:10.1371/journal.pone.0018042.

Higham, James P., Michael Heistermann, and Dario Maestripieri. 2011. "The Energetics of Male–Male Endurance Rivalry in Free-Ranging Rhesus Macaques, *Macaca mulatta*." *Animal Behaviour*, 81: 1001–1007. DOI:10.1016/j.anbehav.2011.02.001.

Poretsky, Leonid, and Marcia F. Kalin. 1987. "The Gonadotropic Function of Insulin." *Endocrine Reviews*, 8: 132–141. DOI:10.1210/edrv-8-2-132.