IGF-1: a marker of individual life-span in a primate

Fabienne Aujard,[1] Marie Thérèse Bluet-Pajot,[2] Philippe Zizzari,[2] Martine Perret,[1] Jacques Epelbaum[2]

[1]UMR CNRS/MNHN7179, Brunoy, France; [2]UMR 894 INSERM-Paris Descartes, Paris, France

Abstract

The development of biological markers to evaluate individual life-span is badly needed because of the high cost and time duration that are necessary to assess the ageing process in long-living organisms such as primates. In this study, we measured insulin-like growth factor-1 (IGF-1) levels in a small, relatively short-living (maximal longevity: 12 years) primate from Madagascar, the gray mouse lemur (*Microcebus murinus*), in order to determine if they can be related to the rate of survival of this seasonal species. Cross-sectional blood samplings on 112 males of various ages indicated that IGF-1 levels remain high and constant during the long-day breeding seasons while a significant age-related decrease occurs from the fourth short-day resting season onward. Interestingly, in four-year-old lemurs, short-day IGF-1 body mass ratio values appeared as a good predictor of their life-span.

Introduction

Because of the high cost and time duration that are necessary to assess the ageing process, the development of biological markers to evaluate individual life-span is badly needed. Among candidate biomarkers, a decrease in the insulin-like growth factor-1 (IGF-1) transduction pathway appears to play a key role in the control of ageing and longevity in many animal models from *C. elegans* to mammals.[1] In humans as in rodents, plasma IGF-1 levels decrease with ageing but the ageing process per se is often associated with metabolic changes such as increase in fat mass, which also strongly interferes with longevity. Moreover, a recent genetic study in offspring of centenarians reported functionally significant IGF-1 receptor gene polymorphisms that were associated with gender-specific differences in circulating IGF-1.[2]

In a small, relatively short-living (maximal longevity: 12 years) primate from Madagascar, the gray mouse lemur (*Microcebus murinus*), metabolic and physiological parameters exhibit high seasonal changes coupled with an age-related decrease in amplitudes.[3,4] In particular, in males body weight varies widely from the long-day-length summer breeding season, when mouse lemurs display marked behavioral arousal, to the short-day-length winter resting season when reproductive functions stop and animals gain fat. Therefore, we tested whether the gray mouse lemur is an adequate model to determine the relationship between circulating IGF-1 levels, age, and fat mass.

Materials and Methods

Animals

Male gray mouse lemurs (*Microcebus murinus*) used in this study were all born in the laboratory breeding colony (Brunoy, MNHN, France, European Institutions Agreement no. 962773) from a stock originally caught in southern Madagascar 40 years ago. They were kept in controlled conditions with constant ambient temperature (24-26°C), constant relative humidity (55%), and food available *ad libitum*. All experiments were carried out in accordance with the European Community Council Directive (86/609/EEC).

Biological rhythms of mouse lemurs are photoperiod dependent. Exposure to long days (>12h light per day) entrains seasonal activation of behavioral and physiological activities. In contrast, exposure to short days (<12h light per day) leads to pronounced fattening, reduced activity, torpor, and complete sexual rest in both sexes. To ensure highly synchronized changes in biological rhythms within captive individuals, animals were exposed to an artificial photoperiodic regimen consisting of a six-month period of Malagasy winter-like short-day-length (LD 10:14) and a six-month period of Malagasy summer-like long-day-length (LD 14:10). Spontaneous food intake varies from 40-60 Cal/j.100gBW in the fattening period to 10-20 Cal/j.100gBW, a state of "winter anorexia", in mid- and end-winter. The remaining part of the year it ranges between 30 and 40 Cal/j.100gBW. Animals of all ages lived simultaneously under each photoperiodic condition, and blood samples were obtained at least six weeks after light change. Of the 112 animals tested, 95 spontaneously died on average at 7.0±0.2 years old and the longest living individual reached 12.0 years.

Blood sampling and IGF-1 measurement

Approximately 200 µL of saphenous vein blood was drawn from 0.5- to 11-year-old males, either during the summer breeding season (n=60) or during the winter sexual rest (n=52), at a fixed time during the daily sleeping period to minimize circadian variations. Total IGF-1 plasma levels were measured after ethanol extraction by IRMA (Kit IGF1 IRMA ref 3516 Immunotech, France), using human IGF-1 as the standard. All samples were assayed in the same assay. Assay sensibility was 3 ng/mL and intra-assay variability was 4%.

Statistics

All values are given as the mean ± SEM and analyses were conducted using SYSTAT for Windows. Significant differences between short- and long-day values were tested by ANOVA. Relationships between body weight or IGF-1 levels and age were assessed by regression analysis tests.

Results and Discussion

As shown in Figure 1, huge seasonal variations in the body mass were observed in male gray mouse lemurs ranging from 0.5 to 11 years of age (LD: 85.5±1.5 g, n=60 vs SD: 99.4±2.9 g, n=52, Anova F=19.9, $df_{1/110}$, P<0.001). These variations were accompanied by equally huge changes in IGF-1 levels (LD: 461±20 ng/mL, n=60 vs SD: 241±14 ng/mL, n=52, F=75.2, $df_{1/110}$, P<0.001). This difference still held true when taking into account the seasonal variation in body weight (ratio IGF-1 ng/mL.100 gBM: 510±14 in LD vs 254±18 ng/mL.100 gBM in SD, F=68.3, $df_{1/109}$, P<0.001). IGF-1 levels were constantly high

Correspondence: Jacques Epelbaum, Centre de Psychiatrie et de Neurosciences, UMR 894 INSERM-Paris Descartes, 2 ter rue d'Alésia, Paris, 75014, France.
E-mail: jacques.epelbaum@inserm.fr

Key words: IGF-1, marker of longevity, primates.

Contributions: all authors were involved in setting up the experiments and discussing the results. FA and MP were responsible for the colony and provided the samples and statistics. MTB and PZ set up the conditions for the IGF-1 assay. JE wrote the manuscript.

Conflict of interest: the authors report no conflicts of interest.

Received for publication: 27 November 2009.
Revision received: 5 March 2010.
Accepted for publication: 14 March 2010.

Ageing Research 2010; 1:e2
doi:10.4081/ar.2010.e2

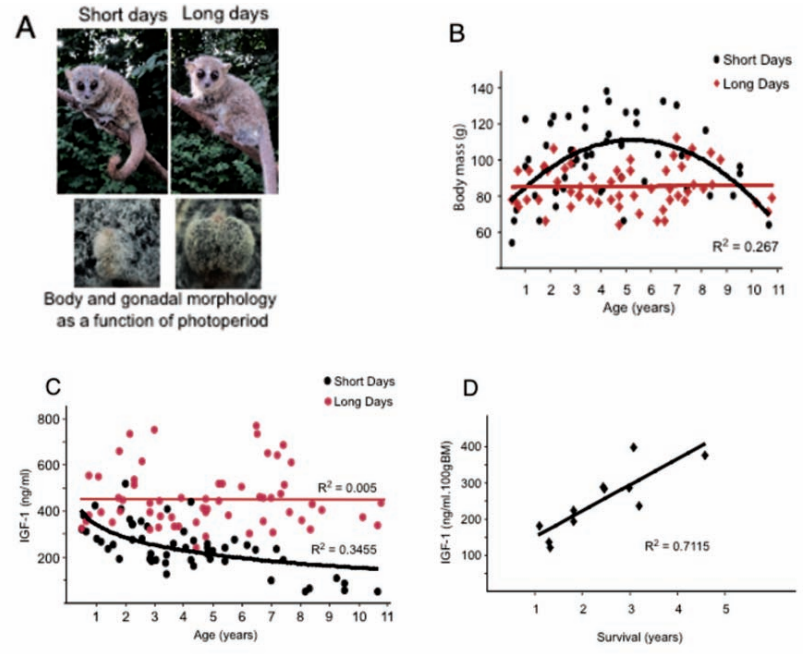

Figure 1. Seasonal variations in body mass and IGF-1 plasma levels as a function of age. Seasonal rhythms depend on the photoperiod (A and B). In short days (day length <12h), reproductive functions stop and the animal gains fat, while in long days seasonal reproduction is associated with behavioral arousal and marked decrease in body mass. IGF-1 levels are expressed seasonally in an inverse manner. Plasma IGF-1 levels (C) are correlated with age during the short-day period only and, in middle-aged (4 years old) individuals, are highly correlated with survival from the time of sampling to spontaneous death (D).

and unrelated to age during the long-day breeding season (R^2=0.004, NS; Figure 1C) but decreased significantly with ageing during the short-day sexual rest (R^2=0.3455, P<0.001; Figure 1C).

Most interestingly, in middle-aged gray mouse lemurs (i.e. 4-years old), plasma IGF-1 levels during short days correlated with the rate of survival expressed as the time between sampling and spontaneous death (R^2=0,4742, n=11, P<0.05; data not shown). The correlation was even higher when the IGF-1/BM ratio was plotted against the survival duration (Figure 1D; R^2=0,7115, P<0.01).

Thus, in the gray mouse lemur, age-associated changes in IGF-1 plasma levels are observed only during the short-day sexual rest period, when body fat is maximal. IGF-1 starts to decrease as soon as the second year of age. This is in striking contrast with two other hormones, dehydroepiandrosterone sulfate (DHEA) and testosterone, the levels of which decline only after six years of age and in the long-day-length season.[4] Indeed, when considering slopes of age-related changes, the earliest and fastest change concerned IGF-1 decrease during the short-day-length season (body mass: 6.9%/year; DHEA: 11.6%/year; IGF-1: 17.4%/year).

Interestingly, when normalized to body mass, IGF-1 in the short-day condition appears as a good marker of individual life-span. Because lean mass remains identical in the two photoperiodic conditions,[5] this indicates that fat mass increase after the first year of life and during adulthood is probably involved in the changes in IGF-1, as also observed in humans. However, in the longest living animals, the ratio of IGF-1/BM is still higher under the long-day conditions than under the short-day conditions even though body weight no longer differs. Thus, it appears that some plasticity in IGF-1 levels remains active in the oldest animals in response to the photoperiod change even though body mass does not change at these older ages. Given the evidence that the IGF-1 system responds to exercise, this plasticity might be related to an increased photoperiod-dependent activity in longer-lived lemurs. Indeed, although some age-related differences in locomotor activity rhythms are observed under short-day-length, they predominate under long-day-length conditions.[6]

In summary, in male gray lemurs: IGF-1 levels remain high and constant during the long-day breeding seasons while a significant age-related decrease occurs from the fourth short-day resting season onward, and only short-day-length IGF-1 values appear as a good predictor of survival of four-year-old lemurs. It has been demonstrated recently that brain IGF-1 receptors control mouse growth and life-span through a neuroendocrine mechanism, allowing individuals to decelerate growth and preserve resources, thereby improving fitness in challenging environments.[7] Thus, we propose the mouse gray lemur as a fascinating animal model to further determine the factors, including IGF-1, that regulate life-span.

References

1. Longo VD, Finch CE. Evolutionary medicine: from dwarf model systems to healthy centenarians? Science 2003;299:342-6.
2. Suh Y, Atzmon G, Cho MO, et al. Functionally significant insulin-like growth factor I receptor mutations in centenarians. Proc Natl Acad Sci USA 2008; 105:3438-42.
3. Giroud S, Blanc S, Aujard F, et al. Chronic food shortage and seasonal modulations of daily torpor and locomotor activity in the grey mouse lemur (Microcebus murinus). Am J Physiol Regul Integr Comp Physiol 2008;294:R1958-67.
4. Perret M, Aujard F. Aging and season affect plasma dehydroepiandrosterone sulfate (DHEA-S) levels in a primate. Exp Gerontol 2005;40:582-7.
5. Giroud S, Perret M, Stein P, et al. The grey mouse lemur uses season-dependent fat or protein sparing strategies to face chronic food restriction. PLoS One 2010;5:e8823.
6. Aujard F, Cayetanot F, Terrein J, et al. Attenuated effects of increased daylength on activity rhythm in the old mouse lemur, a non human-primate. Exp Gerontol 2007;42:1079-87.
7. Kappeler L, De Magalhaes Filho C, Dupont J, et al. Brain IGF-1 receptors control mammalian growth and lifespan through a neuroendocrine mechanism. PLoS Biol 2008; 6:e254.