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Blood glucose concentration in caviomorph rodents

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Abstract

Hystricomorph rodents are a group of species that belong to the suborder Hystricognathi. They mainly inhabit South American (caviomorph) and African (phiomorph) habitats. This group of rodents has a divergent insulin structure. For example, insulin in this group of rodents exhibits only 1–10% of biological activity in comparison to other mammals. Therefore, hystricomorph rodents may hypothetically be unable to regulate blood glucose concentration as non-hystricomorph mammals. In this work we evaluated blood glucose concentration in nine species of caviomorph rodents, with emphasis on species belonging to the families Abrocomidae, Ctenomyidae and Octodontidae. Specifically we: (1) measured glucose concentrations after a fasting period; and (2) conducted a glucose tolerance test. In the latter assay we used *Octodon degus* as a representative species of the genus *Octodon*. Results showed that blood glucose concentration values after fasting, and in the glucose tolerance test, were within the expected range for mammals. We postulate that this group of rodents has compensatory traits that may permit the maintenance of standard values of plasma glucose.

Keywords: Hystricomorph; Caviomorph; Insulin; Blood glucose concentration; Glycemia; Pancreatic hormones; Oral glucose tolerance test; Diabetes

1. Introduction

Blood glucose concentration in mammals is tightly regulated, reflecting a trade-off mainly between two opposing hormones: glucagon and insulin, produced, respectively, by α and β cells in the Langerhans islets of the pancreas. Studies on the structural and physiological diversity of glucagon among mammals are scarce. Interestingly, amino acid sequencing revealed that the glucagon molecule of rodents in suborder Hystricognathi (hereafter hystricomorph) has many amino acid substitutions (Huang et al., 1986; Nishi and Steiner, 1990) that, in turn, affect its physiological performance (Huang et al., 1986). Specifically, the biological activity of glucagon in guinea pig is 10-fold lower than in non-hystricomorph species (Huang et al., 1986). In contrast, in spite of the high diversity of mammals, insulin is a highly conservative protein (Chan and Steiner, 2000; Conlon, 2001). In fact, the regulatory properties of insulin are interchangeable among species. Nevertheless, like glucagon, the insulin of the hystricomorph rodents also exhibits critical amino acid substitutions in comparison to other mammalian species (Smith, 1966, 1972; Neville et al., 1973) affecting its physiological properties (Zimmerman et al., 1974; Bajaj et al., 1986).

The first sign that the insulin of this group had an unusual structure came from experiments showing that guinea pigs produce antibodies to bovine

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insulin without showing hyperglycemia (Moloney and Coval, 1955). It is now known that insulin from hystricomorph rodents is not inactivated by antibodies produced for non-hystricomorph mammals (Davidson et al., 1968, 1969; Neville et al., 1973). In addition, hystricomorph rodent insulin lacks self-associating capacity, does not bind zinc ion, and the distribution and quantity of zinc in the pancreas is different than in non-hystricomorph mammals (Maske, 1957; Zimmerman et al., 1972; Horuk et al., 1980). Moreover, insulin growth promoting property is higher in hystricomorph rodents (Zimmerman et al., 1974; King and Kahn, 1981), whiles its activity for reducing the blood glucose concentration, appears to be only 1–10% in comparison to non-hystricomorph mammals (King and Kahn, 1981). The latter could be explained because the second putative binding site of the insulin molecule, proposed by Schaffer (1994), has been lost in this group of rodents. However, in general, there is agreement between structural divergence and in vitro biological activity (Conlon, 2001).

Although hypoglycemic activity is reduced in vitro, hystricomorph insulin can develop the same maximal response as non-hystricomorph mammals, but at insulin concentrations above standard values and never measured in healthy non-hystricomorph mammals (Zimmerman et al., 1974). Unfortunately, there are no records of insulin concentration in hystricomorph rodents other than *Cavia porcellus* (Davidson et al., 1968, 1969, see Section 4). The fact that hystricomorph insulin reaches the same maximal response as in non-hystricomorph mammals can be produced through changes in binding properties and/or in their intrinsic biological activity (Rodbell et al., 1971). Nevertheless, the requirement of higher insulin concentrations to do it, favors the hypothesis that it is the receptor binding properties that are modified (Zimmerman et al., 1974).

Consequently, we can hypothesize that, given the low physiological activity of hystricomorph insulin, these rodents will be unable to regulate glucose concentrations as tightly as non-hystricomorph mammals. Alternatively, we would expect compensatory traits that permit this hystricomorphs to regulate in the same way as any non-hystricomorph mammal.

Given that hystricomorph rodents have a divergent insulin hormone, we tested whether neotropical species from this suborder, are able to regulate glucose concentrations like other mammalian species. Consequently, the objectives of this work were: (1) to measure blood glucose concentrations in neotropical hystricomorph (hereafter caviomorph) rodents after a fasting period; and (2) to conduct a glucose tolerance test. Species sample was skewed to the families Octodontidae, Ctenomyidae and Abrocomidae. Insulin of the first two families not only presents many amino acid substitutions like others hystricomorphs, additionally, they exhibit an insertion in the A chain, and a deletion in the B chain (Nishi and Steiner, 1990, J.C. Opazo, unpubl. data). Additionally, species from the family Abrocomidae possess an intermediate insulin structure with a deletion of the phenylalanine at position 24 in the B chain, however, they lack the amino acid insertion in the A chain (J.C. Opazo, unpubl. data). Consequently, they could be a group that present potential problems to regulate blood glucose concentration.

Table 1
Caviomorph species included in this study

Order Rodentia
Suborder Hystricognathi
Family Caviidae
Microcavia niata
Family Abrocomidae
Abrocoma bennetti
Family Octodontidae
Aconaemys fuscus
Octodon bridgesi
Octodon degus
Octodon lunatus
Octodontomys gliroides
S. cyanus
Family Ctenomyidae
Ctenomys opimus

2. Material and methods

2.1. Animals and capture

Nine species belonging to four families of caviomorph rodents were used (Table 1). We used both Sherman live traps and padded leg-hold traps to capture animals from seven sites. Using Sherman live traps, we captured 19 males of *Octodon degus*, and 1 male from the rare species *O. lunatus* in Lampa (33°17′S, 70°53′W). Another *O. lunatus* male was collected in Aucó (31°30′S, 71°06′W). Eight females and four males of *O. bridgesi* were

collected in Tregualemu (36°56′S, 71°52′W). Four females and one male of *Octodontomys gliroides* were captured in Chusmiza (19°40′S, 69°10′W), and six females and three males of *Abrocoma bennetti* were collected in Aucó.

Using padded leg-hold traps, we obtained three females and one male of *Microcavia niata* and two females and four males of *Ctenomys opimus* from Colchane (19°17′S, 68°40′W). Three females and two males of *Spalacopus cyanus* were collected in Lagunillas (33°37′S, 70°18′W), and one male of *Aconaemys fuscus* in Rio Teno (34°58′S, 70°56′W).

Animals were transported to the laboratory and maintained with a photoperiod of 12:12 (light:dark) at 23±2 °C. Animals were fed a diet of rabbit food pellets (*O. bridgesi, O. degus, O. lunatus*), a mixed diet of carrots, apples and rabbit food pellets (*A. bennetti, A. fuscus, M. niata* and *O. gliroides*) or only carrots and apples (*S. cyanus* and *C. opimus*), and were provided with water ad libitum, for 2 weeks prior to assays.

2.2. Fasting blood glucose

We first conducted the fasting blood glucose test for all species. According to National Diabetes Data Group, individuals were fasted for 15 h, after which a blood sample was obtained. To evaluate the normality of glycemia, we used the National Diabetes Data Group criteria (1979), because it is the most exigent standard reference for glucose concentration values reported for non-human mammals, including rodents species (Nelson, 1995; Oglesbee, 1996). That is, after a fasting period, blood (capillary) glucose concentrations must be below 5.55 mM to be considered normal.

2.3. Glucose tolerance test

We performed a glucose tolerance test 1 week following the fasting blood glucose test. After 15 h of fasting, each individual ingested, 0.5 ml of a glucose solution containing 0.7 g glucose, via a syringe fitted with a flexible plastic tube. National Diabetes Data Group recommends 1.071 g/kg for a standard human of 70 kg. Among the species assayed in this study, the smallest (*O. gliroides*) received a dose of 5.3 g/kg and the biggest (*M. niata*) received 2.8 g/kg. Blood samples were then taken 120 min after glucose loading.

In this test, we used *O. degus* (eight different individuals) as a representative of the genus *Octodon*. Specifically, in these individuals we took blood samples at 30, 60, 90 and 120 min, to obtain a record of the complete response to glucose loading. The measurements at 120 min were considered as the measure of the glucose tolerance test, and were included in Table 2.

To evaluate the normality of the glycemia after loading, we followed the National Diabetes Data Group criteria (1979), i.e. 2 h after loading, blood (capillary) glucose concentration must be lower than 7.78 mM, and at 30, 60 and 90 min less than 11.11 mM, to be considered normal.

Some animals died in the interval between the two tests (one individual of *S. cyanus* and *O. gliroides,* and two individuals of *A. bennetti*). Furthermore, some animals showed abnormal values in glucose tolerance test (two individuals of *A. bennetti* and one of *M. niata*) and were eliminated from the analyses. Due to these two reasons the number of individuals was not the same between the two tests.

2.4. Glucose concentration values

Blood samples of approximately 40 μl were obtained from the orbital sinus, and the entire sampling procedure did not take longer than 30 s. Glucose concentration measurements were conducted using a Glucometer Elite from Bayer. This system has a measurement range of 1.11–33.33 mM, and requires only 2 μl for an accurate determination with less than 5% error in comparison to clinical assays. All experimental procedures in this article were conducted according to the current Chilean law, and under permit number SAG-698 of the Servicio Agrícola y Ganadero.

2.5. Data analysis

Data were analyzed using one tailed Student *t*-test, comparing the mean of the sample with the National Diabetes Data Group criteria (1979). We did not perform the fasting blood glucose statistical test for *A. fuscus* and *O. lunatus* because we had only one and two individuals, respectively.

3. Results

3.1. Fasting blood glucose

All species exhibited blood glucose concentration below 5.55 mM after 15 h of fasting (Table

Table 2
Blood glucose concentrations after fasting

Species	Fasting blood glucose			Oral glucose tolerance test		
	N	Body mass (g) ± S.D.	Blood glucose (mM) ± S.D.	*N*	Body mass (g) ± S.D.	Blood glucose (mM) ± S.D.
A. bennetti	9	200.56 ± 57.50	3.1 ± 0.43*	5	195.48 ± 43.93	4.33 ± 0.97*
A. fuscus	1	119.5	4.39	1	122.2	3.55
C. opimus	6	231.75 ± 78.89	3.92 ± 0.49*	6	236.98 ± 69.17	4.63 ± 0.69*
M. niata	4	245.08 ± 13.77	4.88 ± 0.4*	3	262.3 ± 5.90	4.54 ± 0.5*
O. bridgesi	12	163.48 ± 26.74	4.06 ± 0.55*	–	–	–
O. degus	11	211.26 ± 39.65	4.34 ± 0.22*	8	199.74 ± 36.08	4.69 ± 0.68*
O. lunatus	2	210.60 ± 22.34	3.69 ± 0.35	–	–	–
O. gliroides	5	131.0 ± 10.09	4.15 ± 0.72*	4	130.5 ± 15.34	4.54 ± 1.53*
S. cyanus	5	137.42 ± 20.21	4.01 ± 0.69*	4	150.9 ± 19.87	3.93 ± 0.7*

Values are mean ± S.D.; *$P < 0.05$.

2). In *A. fuscus* and *O. lunatus*, values were also within mammalian standards.

3.2. Glucose tolerance test

All species assayed showed values below 7.78 mM, 2 h after glucose loading (Table 2). In *O. degus*, measurements taken at 30 ($t_7 = 6.89$, $P < 0.05$), 60 ($t_7 = 19.75$, $P < 0.05$) and 90 ($t_7 = 18.14$, $P < 0.05$) min were below 11.11 mM (Fig. 1).

4. Discussion

At least two alternatives in blood glucose regulation in hystricomorph rodents can be considered: (1) this group has glucose concentration values higher than other mammalian species due to diminished biological activity of its insulin molecule, and as consequence its physiology should change to satisfy this condition; or (2) this group has compensatory mechanisms that allow it to maintain the same blood glucose concentrations as other mammals, and as a consequence, its physiology follows standard mammalian patterns.

In this study, we demonstrated that the caviomorph species assayed exhibit standard mammalian values of glucose concentration. These normal values were obtained after a fasting period, and 2 h after loading in an oral glucose tolerance test. Using *O. degus* as a model we obtained normal values at 30, 60 and 90 min in the same test.

Members of the families Octodontidae and Ctenomyidae, deserve special attention, since they have a special insulin (assuming that all species of the family have the same insulin structure). That is, the A chain has an insertion of two amino acids (Val-Pro) at the carboxy terminal end, and a phenylalanine deletion at position 24 in the B chain (Nishi and Steiner, 1990, J.C. Opazo, unpubl. data). Nevertheless, we observed that species from these families exhibited standard mammalian values of glucose concentration in both tests.

Individuals of *A. bennetti* showed lower values following a fasting period (3.1 ± 0.43 mM), plac-

Table 3
Upper limits for blood glucose concentration after fasting period in non-human mammals

Species name	Blood glucose (mM) (upper limit)	Mammalian order	Source
Canis familiaris	8.7	Carnivora	Nelson (1995)
Felis domesticus	9.0	Carnivora	Nelson (1995)
Mustela sp.	7.4	Carnivora	Oglesbee (1996)
Oryctolagus cuniculus	8.61	Lagomorpha	Oglesbee (1996)
Cavia porcellus	6.94	Rodentia	Oglesbee (1996)
Chinchilla lanigera	6.67	Rodentia	Oglesbee (1996)
Mesocricetus auratus	11.11	Rodentia	Oglesbee (1996)
Mus musculus	13.89	Rodentia	Oglesbee (1996)
Rattus rattus	12.05	Rodentia	Oglesbee (1996)

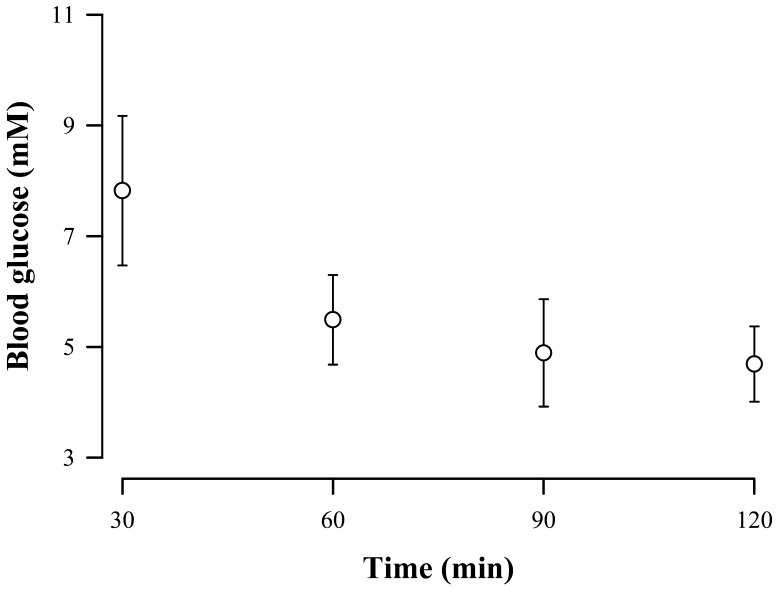

Fig. 1. Glucose tolerance test in *O. degus*. Values represent mean ± S.D.

ing them on the lower limit of normality. This phenomenon is interesting, because the structure of its insulin is an intermediate between the insulin of the families Octodontidae and Ctenomyidae and the family Caviidae. Insulin of *A. bennetti* lacks phenylalanine at position B24, as well as the two amino acid insertion in the A chain (J.C. Opazo, unpubl. data). Unfortunately, no other endocrinological studies are available.

Some individuals (see Section 2), who had normal glucose concentration values after a fasting period, displayed abnormal values in the glucose tolerance test. Specifically, two individuals of *A. bennetti* had 15.72 mM and 12.94 mM, while the only *M. niata* had 14.11 mM. In these cases we repeated the measurements to be sure of the results, and in both species, glucose concentration was again abnormal. According to the standards set by the National Diabetes Data Group (1979) it is possible to diagnose diabetes in these animals. Additionally, the animals presented typical symptoms of diabetes, like obesity and cataracts. These results agree with the fact that several hystricomorph rodent species suffer diabetes (Jansen et al., 1999). Comparative data about glucose concentration values show that their limits vary among mammalian species (Table 3). The caviomorph *C. porcellus* and *C. lanigera*, that conserved the length of the insulin molecule, can regulate their glycemia like a non-hystricomorph mammals (Nelson, 1995; Oglesbee, 1996).

In addition, we recorded values of glucose concentration in *O. degus* in the field. Values were 4.54 ± 0.58 mM, ranging from 3.89 to 5.39 mM ($n = 16$), that is, within the normal mammalian range (Opazo and Soto-Gamboa, unpublished data). These data provide additional support for our laboratory results. Based on the data reported in the literature (Oglesbee, 1996; Kind et al., 2003) and our own results, we hypothesize that the entire suborder Hystricognathi could regulate their glycemia like the caviomorph species assayed here. Additionally, since caviomorph rodents assayed in this study regulate glucose levels like typical non-hystricomorph mammals, we expect mechanism in this group to compensate the reduced biological activity of the insulin.

One such compensatory mechanism explaining this phenomenon is a change in insulin concentrations. Unfortunately, it is difficult to measure insulin concentrations in this group of rodents, because routine determinations with antibodies for non-hystricomorph mammals (e.g. human, bovine) fail to detect hystricomorph insulins (Davidson et al., 1968, 1969). Until now, there was one article reporting a 10-fold higher insulin concentration in *C. porcellus* in comparison with other mammals. However, details regarding the conditions of this

measurement were not reported (Zimmerman et al., 1974). Nevertheless, recently, Kind et al. (2003) measured insulin concentration in guinea pigs. The results showed that compared with non-hystricomorph mammals, *C. porcellus* had an order of magnitude more insulin. This finding supports the view that these animals compensate for the reduced biological activity of their insulin by increasing their insulin concentrations. Additionally, the rate of disappearance and degradation of insulin could also explain our results. In fact, measurements confirm that the rate of disappearance and degradation of insulin in *C. porcellus* is slower than bovine insulin (Zimmerman et al., 1974). This phenomenon is reinforced by the fact that human patients with distortions in insulin molecule, that affect its binding affinity, showed higher insulin concentration and slower degradation rate (Haneda et al., 1984). When an individual cannot respond to its own insulin, because a decreased sensitivity of target cells, they cannot take up glucose as easily as they should, leading to insulin resistance. To compensate this poor response, this syndrome is characterized among others by an increase in insulin concentration. In hystricomorph rodents, insensitivity can be produced by substituted insulin that loses binding affinity and not by changes in the receptor (Zimmerman et al., 1974; Horuk et al., 1979; Bajaj et al., 1986). In fact, when hystricomorph tissue was used in binding affinity experiments, the hystricomorph insulin receptor responded like a non-hystricomorph receptor to mammalian insulin (Zimmerman et al., 1974). Similarly, teleostean fishes have insulin molecules with lowered (30–50%) biological activity, and a slow response to insulin, yet they have normal values for plasma glucose concentrations (Wright et al., 2000).

Alternatively, changes in the insulin receptor may explain the normal glucose values found in hystricomorph rodents. Comparative studies regarding insulin receptors are scarce. The use of antibodies against the α subunit of human insulin has been utilized to find out whether these antibodies are capable of precipitating the receptors of other species. So far, results are not clear, mainly because antibodies cannot precipitate the α subunit in myomorph rodents (Morgan et al., 1986; Soos et al., 1986). Nevertheless, Tong et al. (1994) reported the precipitation of the *C. porcellus* insulin receptor, but not that of *Chinchilla lanigera*, another caviomorph rodent. This last finding is particularly interesting because the insulin of *C. lanigera* is less divergent than the insulin of *C. porcellus*, in comparison to other mammals (Horuk et al., 1979).

Studies on the β subunit are even scarcer. Nevertheless, the immunological results are more consistent. Antibodies designed against the β subunit showed less variation, and were able to recognize all species assayed (Morgan et al., 1986; Soos et al., 1986). This suggests an evolutionary constancy in the signal transduction mechanism of insulin among all of the groups examined, and other taxa (Muggeo et al., 1979; Garofalo, 2002).

Another way to compensate for the low biological activity of hystricomorph insulin is through the number of receptors (Dufty et al., 2002). Indeed, Muggeo et al. (1979) found an inverse relationship between the biological activity of insulin and the number of receptors. At one extreme was the guinea pig (a caviomorph rodent), which showed biological activity 1–10% that of other mammals, with the highest number of receptors. On the other side, were birds, with biological activity two-fold higher than mammals, and a five-fold lower number of receptors (Simon et al., 1977; Navarro et al., 1999). Increasing the number of receptors as a compensatory mechanism is reinforced by the fact that the insulin receptor of birds has functional characteristics similar to those of mammals (Ginsberg et al., 1977). The idea of a compensatory mechanism in endocrinology is not novel, and it is not surprising to observe this phenomenon in this group of rodents (Haneda et al., 1984; Hadley, 1992; Dufty et al., 2002).

Finally, it is not clear to us why hystricomorph insulin diverges in its structure and physiological performance. Since, in terms of glucose concentration, hystricomorph rodents behave like other mammals, it is possible to postulate that changes in insulin structure may reflect the acquisition of an alternative function. In fact, King et al. (1983) found that hystricomorph insulin can bind to the receptor of platelet derived growth factor (PDGF), and this binding is not affected by the presence of porcine insulin or insulin growth factors (IGF's), but it is affected by hystricomorph insulin and PDGF. These data suggest that the insulin of hystricomorph rodents can bind to a receptor that does not bind any other insulin molecule, and that the cellular growth function of hystricomorph insulin is achieved in another way.

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References

Bajaj, M., Blundell, T.L., Horuk, R., Pitts, J.E., Wood, S.P., Gowan, L.K., et al., 1986. Coypu insulin. Biochem. J. 238, 345–351.

Chan, S.J., Steiner, D.F., 2000. Insulin through the ages: phylogeny of a growth promoting and metabolic regulatory hormone. Am. Zool. 40, 213–222.

Conlon, J.M., 2001. Evolution of the insulin molecule: insights into structure-activity and phylogenetic relationships. Peptides 22, 1183–1193.

Davidson, J.K., Zeigler, M., Haist, R.E., 1968. Failure of guinea pig antibody to beef insulin to neutralize coypu (Nutria) insulin. Diabetes 17, 8–12.

Davidson, J.K., Zeigler, M., Haist, R.E., 1969. Failure of guinea pig antibodies to beef insulin, chicken insulin and cod insulin to neutralize capybara insulin. Diabetes 18, 212–215.

Dufty Jr, A., Clobert, J., Moller, A.P., 2002. Hormones, developmental plasticity and adaptation. TREE 17, 190–195.

Garofalo, R.S., 2002. Genetic analysis of insulin signaling in *Drosophila*. TEM 13, 156–162.

Ginsberg, B.H., Kahn, C.R., Roth, J., 1977. The insulin receptor of the turkey erythrocyte: similarity to mammalian insulin receptors. Endocrinology 100, 82–90.

Hadley, M.E., 1992. Endocrinology. Prentice Hall Publ, New Jersey.

Haneda, M., Polonsky, K.S., Bergenstal, R.M., Jaspan, J.B., Shoelson, S.E., Blix, P.M., et al., 1984. Familial hyperinsulinemia due to a structurally abnormal insulin. N. Engl. J. Med. 310, 1288–1294.

Horuk, R., Goodwin, P., O'Connor, K., Neville, R.J.W., Lazarus, N.R., Stone, D., 1979. Evolutionary change in the insulin receptors of hystricomorph rodents. Nature 279, 439–440.

Horuk, R., Blundell, T.L., Lazarus, N.R., Neville, R.J.W., Stone, D., Wollmer, A., 1980. A monomeric insulin from the porcupine (*Hystrix cristata*), an old world hystricomorph. Nature 286, 822–824.

Huang, C.-G., Eng, J., Pan, Y.-C.E., Hulmes, J.D., Yalow, R.S., 1986. Guinea pig glucagon differs from other mammalian glucagons. Diabetes 35, 508–512.

Jansen, U., Phillips, A.O., Floege, J., 1999. Rodent models of nephrology associated with type II diabetes. J. Nephrol. 12, 159–172.

Kind, K.L., Clifton, P.M., Grant, P.A., Owens, P.C., Sohlstrom, A., Roberts, C.T., et al., 2003. Effect of maternal feed restriction during pregnancy on glucose tolerance in the adult guinea pig. Am. J. Physiol. 284, R140–R152.

King, G.L., Kahn, C.R., 1981. Non-parallel evolution of metabolic and growth-promoting functions of insulin. Nature 292, 644–646.

King, G.L., Kahn, C.R., Heldin, C.-H., 1983. Sharing of biological effect and receptors between guinea pig insulin and platelet-derived growth factor. Proc. Natl. Acad. Sci. USA 80, 1308–1312.

Maske, H., 1957. Interaction between insulin and zinc in the islets of Langerhans. Diabetes 6, 335–341.

Moloney, P.J., Coval, M., 1955. Antigenicity of insulin: diabetes induced by specific antibodies. Biochem. J. 59, 179–185.

Morgan, D.O., Ho, L., Korn, L.J., Roth, R.A., 1986. Insulin action is blocked by a monoclonal antibody that inhibits the insulin receptor kinase. Proc. Natl. Acad. Sci. USA 83, 322–328.

Muggeo, M., Ginsberg, B.H., Roth, J., Neville, D.M., DeMeyts, P., Kahn, C.R., 1979. The insulin receptor in vertebrates is functionally more conserved during evolution than insulin itself. Endocrinology 104, 1393–1402.

National Diabetes Data Group, 1979. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28, 1039–1057.

Navarro, I., Leibush, B., Moon, T.W., Plisetskaya, E.M., Baños, N., Méndez, E., et al., 1999. Insulin, insulin-like growth factor-I (IGF-I) and glucagon: the evolution of their receptors. Comp. Biochem. Physiol. B 122, 137–153.

Nelson, R.W., 1995. Diabetes mellitus. In: Ettinger, S.J., Feldman, E.C. (Eds.), Textbook of Veterinary Internal Medicine. W.B. Saunders, Philadelphia, pp. 1510–1537.

Neville, R.J.W., Weir, B.J., Lazarus, N.R., 1973. Insulin of hystricomorph rodents. Diabetes 22, 851–853.

Nishi, M., Steiner, D.F., 1990. Cloning of complementary DNAs encoding islet amyloid polypeptide, insulin and glucagon precursors from a new world rodent, the degu, *Octodon degus*. Mol. Endocrinol. 4, 1192–1198.

Oglesbee, B.L., 1996. Enfermedades de las aves y de los animales exóticos de compañía. In: Birchard, S.J., Sherding, R.G. (Eds.), Manual Clínico De Pequeñas Especies. McGraw Hill Interamericana, Mexico, pp. 1481–1687.

Rodbell, M., Birnbaumer, L., Pohl, S.L., Sundby, A.F., 1971. The reaction of glucagon with its receptor: evidence for discrete regions of activity and binding in the glucagon molecule. Proc. Natl. Acad. Sci. USA 68, 909–913.

Schaffer, L., 1994. A model for insulin binding to the insulin receptor. Eur. J. Biochem. 221, 1127–1132.

Simon, J., Freychet, P., Rosselin, G., 1977. A study of insulin binding sites in the chicken tissues. Diabetologia 13, 219–228.

Smith, L.F., 1966. Species variation in the aminoacid sequence of insulin. Am. J. Med. 40, 662–666.

Smith, L.F., 1972. Amino acid sequences of insulin. Diabetes 21, 457–460.

Soos, M.A., Siddle, K., Baron, M.D., Heward, J.M., Luzio, J.P., Bellatin, J., et al., 1986. Monoclonal antibodies reacting with multiple epitopes on the human insulin receptor. Biochem. J. 235, 199–208.

Tong, Z.-Q., Jack, E., Moule, M., Goldfine, I.D., Yip, C.C., 1994. Rodent insulin receptors are immunologically different

from other mammalian insulin receptors. Gen. Comp. Endocrinol. 94, 374–381.

Wright Jr, J.R., Bonen, A., Conlon, J.M., Pohajdak, B., 2000. Glucose homeostasis in the teleost fish tilapia: insights from brockmann body xenotransplantation studies. Am. Zool. 40, 234–245.

Zimmerman, A.E., Kells, D.I.C., Yip, C.C., 1972. Physical and biological properties of guinea pig insulin. Biochem. Biophys. Res. Commun. 46, 2127–2133.

Zimmerman, A.E., Moule, M.L., Yip, C.C., 1974. Guinea pig insulin. II. Biological activity. J. Biol. Chem. 249, 4026–4029.