Alzheimer's disease in humans and other animals; a consequence of post-reproductive lifespan and longevity rather than ageing

Danièlle Gunn-Moore[1], Oksana Kaidanovich-Beilin[2], María Carolina Gallego Iradi[3], Frank Gunn-Moore[4] and Simon Lovestone[5]

1. University of Edinburgh, Royal (Dick) School of Veterinary Studies and The Roslin Institute, Easter Bush Campus, Roslin, EH25 9RG, UK
2. Previously at: Samuel Lunenfeld Research Institute, Toronto, Canada
3. University of Florida, College of Medicine, Department of Neuroscience, Center for Translational Research in Neurodegenerative Diseases, Gainesville, FL 32611, USA
4. University of St Andrews, School of Biology, St Andrews, KY16 9TF, UK
5. University of Oxford, Department of Psychiatry, Oxford, OX3 7JX, UK

Abstract

Two diseases of the modern world – Alzheimer's and diabetes mellitus – are linked by epidemiology, genetics and molecular pathogenesis. They may also be linked by the remarkable observation that insulin signaling sets the limits on longevity. In worms, flies and mice, disrupting insulin signaling increases lifespan leading some to speculate that caloric restriction might extend lifespan in man. It is our contention that man is already a long lived organism, specifically with a remarkably high post-fertility life span, and that it is this that results in the high prevalence of Alzheimer's and diabetes. We review evidence for this hypothesis that carries specific predictions including that other animals with exceptionally long post-reproductive lifespan will have increased risk of both diabetes and Alzheimer's disease and present novel evidence that Dolphin, like man, an animal with exceptional longevity, might be one of the very few natural models of Alzheimer's disease.

Main text

Diabetes mellitus and Alzheimer's disease

As populations all over the world age, enormous challenges are posed by chronic disorders such as Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). Alzheimer's disease in particular is a devastating condition. With a long prodromal period of perhaps ten to twenty years followed by another decade of clinical symptoms, AD and related dementia conditions are becoming a priority for many governments, not least as it is estimated that 1% of global GDP is spent on dementia care (http://www.alz.co.uk/research/files/WorldAlzheimerReport2010.pdf). As well as growing older, the populations of the developed economies are also growing obese and sedentary. Whilst this is most marked in the developed nations, it is truly an international trend and as children in particular show dramatic increases in body mass index, this is a deeply concerning indicator of health problems to come. These health problems are significant as obesity increases risk of cancers, cardiovascular disease and metabolic syndromes including T2DM.

These two health challenges – an ageing population at risk of neurodegenerative disease such as AD, and an increasingly obese population at risk of metabolic conditions such as T2DM – may seem unconnected and unfortunate consequences of modern civilization. It could be suggested that improved health care and sanitation leading to older populations, combined with seemingly unlimited access to highly processed and calorific foods and an increasingly sedentary lifestyle suggests entirely independent and environmental, or more specifically social and historical, causes of the twin challenges of AD and T2DM. It is our contention however, that this construct is only partially explanatory and that there is a molecular link between longevity and both AD and T2DM that suggests a relationship

whereby both arise not as an unfortunate consequence of growing older in the modern world, but are intrinsic to it. In other words that AD and T2DM are conditions not of ageing as they are usually considered, but of longevity. It is not so much how long an organism lives for that governs whether the organism is vulnerable in particular to AD, but the molecular mechanisms that underlie this period; a period that is highly characteristic for any given species. Moreover, that this longevity-associated disease risk explains why AD and T2DM are disorders principally of man. Here we propose a hypothesis that AD and T2DM are the price we pay for the molecular underpinning that allows us to be *almost uniquely* long-lived animals.

Alzheimer's disease is a form of dementia characterised by two main pathological lesions, the amyloid plaque and the neurofibrillary tangle. Whilst it remains contentious whether these lesions are themselves causative of the neuronal loss that results in functional deficits or whether they are simply indicative of an underlying process, the evidence from molecular genetics and experimental neuroscience is compelling that the amyloid cascade is at the heart of the pathology of AD [1]. This cascade involves first the generation of beta amyloid (Aβ) from the Amyloid Precursor Protein (APP) and subsequently the aggregation of highly phosphorylated tau protein. Other processes including neuroinflammation clearly play a role, perhaps to exacerbate the amyloid cascade, perhaps triggered by the cascade or perhaps independently. In addition to genetic causes of familial early onset AD and genetic influences on late onset AD, a considerable effort has been expended on searching for environmental influences on AD. Despite this, relatively few have been identified and arguably, other than age itself only two – head injury and obesity/diabetes – have been unambiguously replicated [2, 3]. The evidence that diabetes and obesity increase the risk of dementia has been consistently reported from many epidemiological

studies, themselves the subject of multiple systematic reviews [4-9]. The mechanism underlying this risk might be at multiple levels, the most parsimonious of which might be that metabolic complications increases vascular damage to the brain and this either exacerbates AD pathology or is an additive or independent insult [3]. However, insulin resistance predicts the development of cerebral amyloid pathology as measured by PET imaging [10] and considerable evidence from cell and animal models suggests that a failure of insulin signaling directly contributes to AD pathological processes, including the formation of tau pathology as we discuss below.

Insulin actions: role of Glycogen Synthase Kinase – 3 (GSK-3)

For a failure of insulin signaling to effect the risk of AD directly rather than through a mediating factor such as vascular damage, then insulin resistance in the periphery should be reflected in insulin resistance in the brain. Considerable evidence suggests that this is in fact the case [11-13]. For example, in mid-life, peripheral insulin resistance is associated with central glucose metabolic abnormality as well as with poorer cognitive performance [14, 15] and predicts amyloid deposition [10]. In turn, there is evidence that central insulin signaling failure or abnormality can induce peripheral insulin resistance. In mice, ablation of insulin receptors (IR) either from the whole brain (neuronal-specific IR knockout, NIRKO) or specifically from hypothalamus or midbrain dopamine neurons, induces hyperphagia, body weight gain, and peripheral insulin resistance [16],[17],[18]. Also, brain-specific genetic inactivation of the insulin receptor substrate 2 (IRS2) that is essential for insulin signaling, results in obesity and diabetic phenotypes [19].

These data demonstrate a critical link between the CNS and the periphery and, importantly, both mice lacking the neuronal insulin receptor and those with IRS2 deleted

are characterized by elevated tau phosphorylation and cognitive alterations, both characteristics of AD [20, 21]. Moreover, animal models of aspects of AD pathology show dysregulated metabolism [22] providing further experimental evidence for an intertwining of the molecular mechanisms of metabolic function and insulin signaling with AD. This link, and the increased risk of dementia in people with diabetes, suggests that there may be therapeutic opportunities for AD in enhancing insulin signaling, or tackling insulin resistance. Real-world data studies suggest that the commonly used therapy for T2DM, Pioglitazone a PPARγ agonist that enhances insulin signalling, reduces the incidence of AD, [23] and intranasal insulin beneficially alters APP processing and reduces cognitive impairment in early AD [24-26]. Large-scale trials of both intranasal insulin and pioglitazone are now underway. Whilst the outcomes of these trials are some years away it is clear that systemic insulin signaling disruption increases the risk of AD and might do so through shared molecular mechanisms and not simply through end-organ damage as a consequence of vascular or other T2DM-induced pathology.

One such molecular mechanism that might plausibly underlie this link between insulin signaling in the brain and AD processes is mediated by Glycogen Synthase Kinase-3 (GSK-3) initially discovered through its ability to phosphorylate glycogen synthase [27]. Given its critical role in insulin signaling it is not surprising that GSK-3 has been implicated in the pathogenesis of obesity and insulin resistance [28, 29], but it has also been shown to have a fundamental role in the pathogenesis of AD [30, 31]. Tau is a physiological substrate of GSK-3 and transgenic mice with increased GSK-3 activity have neurodegeneration phenotypes including tau hyperphosphorylation and cognitive impairments [32]. Even before neurodegeneration sets in, GSK-3 over-activity suppresses long term potentiation (LTP) [33], whilst inhibition of GSK-3 is required following LTP to

block long term depression (LTD) [34] suggesting that the normal regulation of GSK-3 is essential for synaptic plasticity [35]. If GSK-3 is altered in AD, then early neuronal dysfunction could be a consequence of this disruption of plasticity before tau becomes phosphorylated, aggregated and participates in pathological spread.

Given the role of GSK-3 in synaptic plasticity, as well as other functions of neurons such as axonal transport [36] then it is not surprising that these functions become perturbed in the context of metabolic dysfunction such as insulin resistance, resulting in neuronal dysfunction and – for example – cognitive impairment. The finding that a failure of insulin signaling also results in AD pathology are in line with the concept that these neuropathological features represent a final common pathway of disease with multiple influences including in this context insulin signaling but also potentially other processes such as a failure of calcium homeostasis for example [37].

Insulin signaling as a key regulator of longevity

This evidence powerfully argues for a role of insulin signaling and its downstream molecules, in particular perhaps GSK-3, in AD pathogenesis. It would explain, in part, the epidemiological evidence that insulin resistance conditions such as T2DM are risk factors for AD. Insulin signaling however is also, remarkably, associated with longevity. In worms, flies and mice, perturbations in insulin signaling leading to decreased insulin response also lead to a substantially increased lifespan [38-41]. The increase in life span is considerable – in some animals a fold change in normal longevity and in mammals up to a 50% increase. Both caloric restriction resulting in a decreased responsiveness of the insulin signaling pathway and direct knock-out of insulin signaling and associated pathway genes have this effect. The effect is so large, and so consistent, that there are reports of people

attempting to extend their own lives through caloric restriction and many web-sites offer advice on how to do this with various levels of warning about the potential dangers of partial-starvation diets. Clearly there is much to recommend avoiding obesity or even the moderate over-weight state that is becoming the norm in the industrialized nations. Moreover, there is consistent evidence from two long primate studies and one long canine study for the benefits of caloric restriction on health, although they differ on whether caloric restriction increases lifespan in monkeys and dogs as it does in mice [42-45]. However, it remains to be seen, and remains highly controversial, as to whether caloric restriction will have effects on longevity in man.

Man as an exception to the longevity thesis

We believe that this argument, which regularly escapes into the non-scientific general media, is missing an important observation. Man is not like most other animals. Specifically, humans have a notably extended post-fertility lifespan (PFLS). Whilst some life beyond fertility is not uniquely human, indeed it is a characteristic shared with many mammalian species, as Cohen in his review of the relevant literature points out [46]. Nonetheless, even evaluating Cohen's own review data, it is clear that as a proportion of total life span, humans have a remarkable and highly extended PFLS. Women cease to become fecund at a maximum age of ~45 years and lifespan in man is recorded to 110 years and above. Also from Cohen's review only one other animal was identified with an extended PFLS similar to man – the killer whale, *Orcinus Orca*, which has a total lifespan of twice the fertility span (see reference [46] Table 1). Theories abound regarding why man has such a remarkably extended PFLS, the most popular of which is the 'grandmother hypothesis' variants of which suggest an evolutionary advantage to having members of a close-knit hunter-gatherer unit available for child caring and other societal functions [47].

Recently, similar reasoning has been extended beyond man to that other mammal with extended PFLS, Orcinus Orca [48-50], with a model demonstrating that improved reproductive success in younger individuals combined with the usefulness of non-fertile related individuals provides a selection pressure that could account for the evolution of menopause and an extended post-fertility life [51].

However, regardless of the evolutionary origins of PFLS, the link between longevity and the insulin signaling pathway and between insulin signaling and AD suggests a hypothesis. This is that increasing longevity is achieved through increases in PFLS, the molecular underpinning of which is a reduced 'efficiency' of insulin and IGF signaling (IIS) and as a consequence of this reduced IIS, organisms with relatively increased PFLS are at relatively increased risk of AD. In such a hypothesis, the 'efficiency' of IIS might refer to decreased tonic activity or control over the pathway or decreased response, for example, of insulin to metabolic stimulus or of cell response to signaling, or some combination thereof. Whatever the specific mediators of the general mechanism of 'efficiency of IIS', the hypothesis we propose here brings some specific predictions. Most obvious, and most testable, is the prediction that the molecular and pathological characteristics of AD will be more common in animals with a relatively longer PFLS as a proportion of total lifespan. In other words, that plaques and tangles and associated molecular events will be correlated not with age *per se* but with longevity. We would predict the features of AD to be associated more with PFLS than with lifespan and to be a disease not only of man but of other animals with a long PFLS. Specifically, to be a disease in animals such as Orca more than of our closer relatives, such as the Chimpanzee.

Do cetaceans, or other diving animals, have dementia?

We are unaware of any data on AD pathology, let alone cognitive and functional impairment in Orca. However, a related cetacean, *Stenella coeruleoalba*, the striped dolphin, has an average lifespan of ~58 years, and the females drop fecundity at 30 years giving them a PFLS of ~ 48 (Prof V Janik, Scottish Oceans Institute, University of St Andrews, personal communication), similar to the killer whale. Therefore, we set out to examine this hypothesis predicting that an animal with a long PFLS would have evidence of AD pathology hitherto not identified in free living, wild animals. To do this, we obtained, 8 brains from stranded dolphins from different coastal areas of Spain. RNA extraction from this material allowed the identification of the coding region of the APP gene covering the 40-43 amino acid region of the Aβ peptide and was shown to be identical across 3 species of dolphins, *Tursiops truncatus* (bottlenose dolphin), *Grampus griseus* (Risso´s dolphin) and *Stenella coeruleoalba*, and man (Fig. 1A) suggesting that these species of dolphins could generate Aβ from the precursor protein. Three specimens belonging to *Stenella coeruleoalba* species were immuno-positive for amyloid plaques and 4 (3 *Stenella coeruleoalba* and 1 *Tursiops truncatus*) for tau fibrillary tangles. Specifically, 2 types of amyloid deposits were visualised: firstly in the parietal cortex as diffuse deposits, and secondly in the cerebellum, the region of the brain used for echo-location, where there were structures that resembled more compact senile plaques (Fig. 1B). These latter amyloid deposits were up to 50 μm in diameter and in some areas the plaques were relatively numerous. Neurites surrounding these plaques were immunopositive for tau, similar to that seen in cortical amyloid deposits in humans. In the frontal cortex, as well as in the parietal cortex, thalamus and cerebellum, there was evidence of tau pathology, for example, seen as well-defined neurofibrillary threads in the cortex of an adult animal (Fig. 1C). In summary, these studies found evidence of both amyloid deposits and tau pathology in stranded dolphins including in the same individuals (see for example Figure

1E), making this animal one of very few naturally occurring models of an almost uniquely human disease. Clearly it would be of considerable interest to know whether the pathology we observe in these animals had effects on cognition and indeed on behaviour and although such studies are unlikely to be achievable in wild animals, it may be possible to determine the relationship between AD-like pathology and function in captive individuals. We note also with considerable interest that dolphins are also prone to T2DM, showing blood based indicators of insulin resistance [52] and possibly being a natural model of metabolic syndrome [53]. Whilst this is in line with our hypothesis we cannot know if the individuals in this case had such deficits in insulin signaling and response in part because the reference values for dolphin are less certain and in part because analysis of post-mortem samples for analytes such as glucose and insulin is challenging in man [54, 55] and, to our knowledge, not informative in cetaceans.

These findings suggest that full AD pathology – as well as T2DM - can occur in free-living, wild cetaceans. In addition, recent evidence suggests other changes, perhaps indicative of early AD, can be found in other sea mammals. Investigating the stranding and death of sea-lions suffering from domoic acid toxicosis due to blue-green algae, it has been reported that CSF from these animals shows evidence of changes indicative of neurodegeneration [56]. Using untargeted mass spectrometry proteomics methods, Neely *et al* found an excess of multiple complement proteins and gelsolin, proteins we and others have reported to be associated with AD [57, 58]. Other proteins found in the CSF of these animals include Neuronal Cell Adhesion Molecule and Reelin, both proteins previously having been implicated in AD pathology [59, 60]. Even more remarkably to our mind is the observation of altered Dickkopf 3 protein (DKK3) in sea lion CSF in that study. This is of considerable interest as the DKK proteins are the predominant negative regulators of wnt

signaling, the final effector of which is GSK-3 suggesting a possible link to both insulin signaling and to AD pathogenesis. Evidence for a role of DKK in AD abounds. DKK1 is increased by Aβ in human brain and in animal models [61], inhibition or silencing DKK1 prevents Aβ induced synaptic loss [62] and we have shown DKK induction by Aβ transmits the toxic signal through clusterin to not only neurotoxicity but also tau phosphorylation and cognitive impairment [63]. Not surprisingly, given these findings, DKK1 is now of considerable interest as a target for therapy [64]. Most of these studies have focused on DKK1 but not excluded the involvement of the other, highly similar, DKK proteins; however, in at least one study DKK3 co-localised with Aβ pathology in AD brain [65] and was increased in CSF and plasma of people with AD [66].

Alzheimer's disease; just how common is it (in other animals)?

The finding of both amyloid and tau pathology in dolphins, as we report above, is all the more remarkable an observation as AD pathology has only been rarely reported in other mammals [67]. In a recent, detailed and comprehensive review of the ageing brain in non-human animals Youssef et al [67] find evidence of **some** features of human neurodegenerative disease in many animals although note considerable differences from human disease and the absence of a natural model linking the twin features of AD (plaques and tangles) with each other and neuronal loss and with cognitive impairment. Specifically, they note that highly phosphorylated tau but not NFTs are found in sheep, goats, cheetah, bison, baboon, and bears. Closer to man, non-human primates, including Chimpanzee, Orangutan, Gorilla, Baboon, Rhesus, Cynomolgus and Green monkeys are all found to have amyloid plaques but not NFTs (Youssef et al Table 1 [67])

Just as in many of these animals, previous studies have found evidence in dogs (cross-breeds and beagles) of amyloid, but not tau pathology [67]. Cohen (Table 1) indicates that dogs (beagles) have a PFLS of 23.3, though in reality this is breed specific [68, 69], and some families of beagles may be prone to premature senility and develop amyloid deposits but not neuritic plaques [70, 71]. Our hypothesis that PFLS associates with AD pathology would predict that breeds with a longer PFLS than Beagle would be likely to have more AD pathology including neuritic plaques.

The domestic cat has a longer PFLS than dog, of 38 or more (Gunn-Moore, 2016 personal experience), and with reference to T2DM show pathology signs more akin to humans than any other non-primate[72]. Moreover, cats develop early amyloid changes but not plaques [73, 74] although In unpublished findings noted in Youssef et al [67], Nakayama reports neuronal cell loss in the hippocampus of aged cats associated with NFTs composed of highly phosphorylated tau. In a recent comprehensive neuropathological study, Chambers et al, quite remarkably, found the full extent of AD pathology and proposed the cat as a natural model of Alzheimer's [75].In the context of the cat, many pet animals are neutered, and as such their fecundity will have been dramatically reduced, while their PFLS will have been markedly increased. Importantly, neutering increases not only longevity in our pets but also their risk of obesity, and as indicated above in relation to cats, an increase in T2DM. It is not known whether this increase in obesity and T2DM in neutered animals reflects the critical change in 'IIS efficiency' we postulate to be the molecular mechanism underlying the association between PFLS and AD or whether it is central as well as systemic. However, our hypothesis would suggest that, to the extent that it does, then evidence of AD pathology would be present in aged neutered cats. Just as inter-breed

studies in dog might be a means to test the hypothesis then studies in neutered cats might be a means to test the underlying molecular mechanisms.

Conclusions and some suggestions for further study

In summary then, the findings we report and review here suggest that, almost uniquely other than in man, sea mammals and cats might have AD-like neurodegeneration. This ranges from sea lions with domoic acid toxicosis having CSF markers also found in AD, to post-mortem amyloid and tau pathology in the brains of dolphins. Moreover dolphins are uniquely prone to a (pre-) diabetes state and are one of the few animals, alongside other cetaceans and man with a naturally long post-fertility lifespan. Cats have both T2DM and recent evidence suggests, full AD pathology and also have a moderately long PFLS albeit not as long as man and Orca. Is this sharing of AD pathology, diabetes and PFLS important? We suggest it is and this then is our hypothesis: that humans, at some point in our evolutionary history, acquired an insulin pathway trait characteristic that makes it less responsive to external signaling or less effective in transmitting this signal to targets generally or to GSK3 specifically. This characteristic results in longer life relative to other animals but also the twin diseases of T2DM and AD (Figure 2). This hypothesis does not imply that insulin signaling effects only longevity, nor that the effects of insulin signaling on metabolism, longevity and dementia are necessarily mediated through a single mechanism. Nor even that defects in IIS inevitably result in dementia. Clearly there might be independent mechanisms at play and indeed for such a critical signaling pathway with pleiotropic actions on fundamental processes of physiology it would be surprising if there were not independent influences on processes such as metabolism, longevity and dementia. However, here we postulate a linked mechanism that led us to hypothesize that

animals with unusual longevity would be at risk of both insulin resistance and Alzheimer's disease, a hypothesis that led us to a prediction that cetaceans and cats would have AD pathology - a prediction for which we have provided some proof.

This hypothesis has important consequences for our explanatory constructs of human evolution and also some testable predictions. First, in evolutionary theory there has been a robust debate regarding the PFLS in man with some arguing for the competitive advantages offered by the elder in early human societies – the so-called grandmother hypothesis [76]. Our proposal suggests that this theory might be arguing after the effect and the evolutionary driver may have been at a molecular level and theorists might productively search instead for a competitive advantage offered by a relatively less 'efficient' or responsive insulin and IGF signaling pathway. Secondly, in terms of predictions that follow from our hypothesis, we would suggest that AD and T2DM would be relatively less common in non-human mammals and moreover pathological features of both diseases would occur most often in those animals with a relatively longer PFLS. Some aspects of AD pathology have been reported in a wide range of other animals although in almost all cases this is very incomplete making our report here of both neuritic plaque and tangle pathology in dolphin all the more remarkable. Further studies including large variable biomolecular studies such as those that have recently been reported in sea-lion will be of interest in exploring the relationship between AD pathology and vulnerability to metabolic dysfunction in sea mammals and cats. However, testing the prediction that follows from our hypothesis quantitatively from such case reports from wild cetaceans is difficult and we would not advocate the use of captive cetaceans as experimental animals. So we propose a specific experiment. Recombinant inbred strain mice show both variation in lifespan and lifespan response to caloric restriction [77]. Our hypothesis would suggest

that these traits would be associated with insulin signaling phenotypes and moreover, and more surprisingly, with phenotypes relevant to Alzheimer's disease such as Aβ generation, tau expression and phosphorylation. Finally, a word to those individuals practicing caloric restriction to extend lifespan. If we are right, then it's too late; we are already long-lived animals and the price we pay is Alzheimer's disease.

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Competing interests

The authors declare no competing interests.

Display items

Table 1: Lifespan and reproductive span across a range of animals (adapted from Cohen [46])

Cohen (1994) lists the mean Post Reproductive Life Span (PRLS, equivalent to the Post Fertility Lifespan, PFLS, used in the text of this paper and in this table) for a range of animals together with their maximum observed lifespan. Here we extract from Cohen, those where this data is known and have, where a range is given, have listed the mean value and in addition expressed the PFLS as a proportion of lifespan. We add data for man, and assume that 110 is a maximum lifespan, although older people have been recorded, and for PFLS have assumed a mean age at death of 85 years and a mean age of reproductive cessation of 40 years (see http://en.wikipedia.org/wiki/Age_and_female_fertility for discussion of age of fertility).

Figure 1: Alzheimer pathology in striped dolphin (*Stenella coeruleoalba*) brain. **(A)** Aβ42 amino acid alignment between three dolphin species and other mammals. (B) Amyloid plaques in cerebellum tissue from a Stenella coeruleoalba specime, AB2 (Araclon Biotech antibody, 1:750 specific for human beta-amyloid 40); (C) amyloid plaque in parietal cortex from Stenella coeruleoaba AB2 (Araclon Biotech antibody, 1:750 specific for human beta-amyloid 40); (D) neurofibrillary tangles in frontal cortex of Stenella coeruleoalba, 5A6 antibody (Hybridoma Bank, 1:750); (E) neurofibrillary threads and plaques in parietal cortex of a single Stenella coeruleaoba specimen, 5A6 antibody (Hybridoma Bank, 1:750)

Figure 2: Insulin signaling protects against Alzheimer's disease at the cost of longevity

We postulate that for a given stimulus the response of the insulin signaling pathway from generation of ligand through intracellular signaling to the effector of the pathway in the action of GSK3 which is inhibited by insulin signaling, varies giving a relative response that we characterize as 'efficient' or 'inefficient'. Species level differences in the efficiency of response to stimulus will influence the relative lifespan, risk of type 2 diabetes mellitus (T2DM) and risk of Alzheimer's disease (AD); a highly efficient response resulting in relatively shorter lifespan but reduced risk of T2DM and AD whereas a less efficient response increases post fertility lifespan (PFLS) and hence longevity but at the expense of risk of T2DM and AD. Note that this hypothesis emphasizes that the 'efficiency' of the insulin response system is as likely to be the actor in the evolutionary pressure resulting in longevity in man and Orca as the fact that we are both long lived animals.

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Table 1: Lifespan and reproductive span across a range of animals (adapted from Cohen [46])

Order	Scientific Name	Common name	Maximum recorded life span (years)	Mean PFLS (years)	PFLS as a % of maximum lifespan
Artiodactyla	*Bos primigenius*	Cattle	30	5	16.7
	Cervus elaphus	Red deer	21	3	14.3
	Ovis canadensis	Bighorn sheep	19	2	10.5
Artiodactyla	*Canis domesticus*	Domestic dog (beagle)	15	3.5	23.3
Carnivora	*Felis silvestris catus*	Domestic cat	21*	8	38
	Panthera leo	African Lion	17	1.8	10.6
	Ursus maritimus	Polar bear	30	4	13.3
Carnivora	*Globicephalus macrorhyncus*	Short-finned pilot whale	63	14	22.2
Cetacea	*Orcinus orcus*	Killer whale	**78**	**38**	**48.7**
Primates	*Callithrix jacchus*	Common marmoset	10	2	20.0
	Gorilla gorilla	Gorilla	30	4.5	15.0
	Lemur spp.	Lemurs (five spp.)	24	3.5	14.6
	Leontopithecus rosalia	Golden lion tamarin	12	4	33.3
	Macaca fuscata	Japanese macaque	35	4.5	12.9
	Macaca mulatta	Rhesus macaque	35	2.5	7.1
	Macaca nemestrina	Pig-tailed macaque	30	4	13.3
	Macaca radiata	Bonnet macaque	20	6	30.0
	Macaca sylvanu	Barbary macaque	28	5	17.9
	Pan troglodytes	Common chimpanzee	48	9	18.8
	Papio cynocephalus	Olive baboon	27	5	18.5
	Primates Papio cynocephalus /anubis hybrids	Baboon	16	3.5	21.9
	Saguinus fuscicollis	Saddleback tamarin	12	4	33.3
	Saimiri sciureus	Squirrel monkey	19	3.5	18.4
Primates					
Primates	*Homo sapiens*	Man	**110**	**45**	**40.9**

PFLS – post-fertility lifespan.
*But very occasional much older cats have been found – e.g. 32 years of age (seen by author DGM). Importantly, long-lives cats are typically neutered.