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[PubMed Central](#) 1: [Mech Ageing Dev.](#) 2004 Jun;125(6):397-403.[Related Articles, Links](#)**The paradox of the insulin/IGF-1 signaling pathway in longevity.**[Rincon M](#), [Muzumdar R](#), [Atzmon G](#), [Barzilai N](#).

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Ageing may be controlled by a genetic-hormonal system that may have originated from a very early common ancestor. One of the pathways that has been implicated in ageing is the insulin/insulin-like growth factor (IGF-1) signaling, which is involved in many functions that are necessary for metabolism, growth, and fertility in animal models like flies, nematodes, and mammals. While disruption of the insulin/IGF-1 receptor in nematodes and flies increases lifespan significantly, mammals with genetic or acquired defects in insulin signaling pathway are at risk for age-related diseases and increased mortality. This contradiction can be explained by the acquisition of more complicated metabolic pathways in mammals over evolution. Mammals have insulin/IGF-1 receptors in many organs, but their functions are opposite if they are located in the central nervous system or in the periphery; whereas lower species have insulin/IGF-1 receptors signaling mainly through the nervous system. Furthermore, mammals have different and very specific receptors for insulin and IGF-1, with distinct pathways and diverse functions. Striking evidence suggests that decreased IGF-1 levels and signaling during early development, but not the insulin signaling may modulate longevity in many species. Thus, paradoxical outcomes follow the decrease of insulin and/or IGF-1 signal pathway in invertebrates and in mammals, prolonging life in the former and shortening it in the latter. In this review we focus on the downstream cascade of events in the insulin and IGF-1 signaling to identify specific pathways that are relevant to human longevity.

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