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Hypothesis

Insulin/IGF-1 signaling pathway driving aging and cancer as a target for pharmacological intervention

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Abstract

Studies in mammals have led to the suggestion that hyperglycemia and hyperinsulinemia are important factors both in aging and in the development of cancer. Insulin/insulin-like growth factor 1 (IGF-1) signaling molecules that have been linked to longevity include DAF-2 and InR and their homologues in mammals, and inactivation of the corresponding genes followed by the increase in life span in nematodes, fruit flies and mice. It is possible that the life-prolonging effect of calorie restriction is due to decreasing IGF-1 levels. A search of pharmacological modulators of insulin/IGF-1 signaling pathway mimetic effects of life span extending mutations or calorie restriction could be a perspective direction in regulation of longevity. Some old and new observations suggest that antidiabetic biguanides could be promising candidates for both the life span extension and the prevention of cancer.

Keywords: Insulin/insulin-like growth factor 1 signaling pathway; Longevity; Cancer; Antidiabetic biguanides

1. Introduction

The potential link between aging and insulin/insulin-like growth factor 1 (IGF-1) signaling has attracted substantial attention during last years, on the basis of evidence including age-related increase in incidence of insulin resistance and type 2 diabetes in accelerated aging syndromes and life span extension by caloric restriction in rodents. Concomitant reduction in plasma insulin and plasma glucose levels, which implies increases sensitivity to insulin, emerges as a hallmark of increased longevity (Bartke et al., 2003; Tatar et al., 2003). Hyperglycemia is an important aging factor involved in generation of advanced glycosylation endproducts (AGEs) (Facchini et al., 2000a; Ulrich and Cerami, 2001). There are evidence that hyperinsulinemia favors accumulation of oxidized protein by reducing its degradation as well as facilitates protein oxidation by increasing steady-state level of oxidative stress (Facchini et al., 2000a). Untreated diabetics with elevated glucose levels suffer many manifestations of accelerated aging, such as impaired wound healing, obesity, cataracts, vascular and microvascular damage (Dilman, 1994). It was shown that centenarians have a preserved glucose tolerance and sensitivity to insulin as well as lower degree of oxidative stress as compared to aged persons (Barbieri et al., 2003).

It is important to stress that hyperinsulinemia is an important factor not only in aging but also in the development of cancer (Dilman, 1994; Colangelo et al., 2002; Gupta et al., 2002).

In organisms ranging from yeast to rodents, both calorie restriction and mutations in insulin/IGF-1 signaling pathway extend life span (Mattison et al., 2000; Bartke et al., 2003; Longo and Finch, 2003; Tatar et al., 2003). The both approaches have some side effects. For example, calorie restriction increases the level of serum glucocorticoids and decreases resistance to infection (Masoro, 2000, 2003) whereas genetic modifications on insulin/IGF-1 signaling pathway cause obesity, dwarfism and cardiopulmonary lesions (Longo and Finch, 2003). Reviewing the available data on the benefits and adverse effects of calorie restriction and genetic modifications Longo and Finch (2003) suggested three categories of drugs which may have potential to prevent or postpone age-related diseases and

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extend life span: drugs that (1) stimulate dwarf mutations and therefore decrease pituitary production of GH; (2) prevent IGF-1 release from the liver, or (3) decrease IGF-1 signaling by the action on either extracellular or intracellular targets. The concept of calorie restriction mimetics is now being intensively explored (Hadley et al., 2001; Weindruch et al., 2001). Calorie restriction mimetics involves interventions that produce physiological and anti-aging effects similar to calorie restriction. The comparison of the effects of genetic and pharmacological modifications of insulin/IGF-1 signaling pathway on the longevity in carcinogenesis in mammals reviewed in this work have shown the critical role of insulin regulation in aging and cancer.

2. Insulin/IGF-1 signaling pathway and longevity in mammals

The intensive investigations in *Caenorhabditis elegans* since 1990s, which have identified insulin signaling components including daf-2, age-1 and daf-16 as the genes whose mutations lead to life span extension shed new light on molecular mechanisms underlying aging (Kenyon, 2001; Bartke et al., 2003; Tatar et al., 2003). In *D. melanogaster*, the mutation modification of genes operating in the signal transduction from insulin receptor to transcription factor *daf*-16 (*age*-1, daf-2, CHICO, InR etc.) are strongly associated with longevity (Kenyon, 2001; Dillin et al., 2002). It was demonstrated that FKHR, FKHRL1 and AFX, which are mammalian homologues of daf-16 forkhead transcription factor, function downstream of insulin signaling and akt/PKB under cellular conditions (Richards et al., 2002; Ramaswamy et al., 2002). However, it is an open question whether insulin signaling components, including forkhead transcriptional factors, play a critical role in aging and longevity in mammals as well as in *C. elegans* and *D. melanogaster*.

Daf-2 and InR are structural homologues of tyrosine kinase receptors in vertebrata that includes the insulin receptor and the insulin-like growth factor type 1 receptor (IGF-1R). It was shown that in vertebrates the insulin receptor regulates energy metabolism whereas IGF-1R promotes growth. Although decreased insulin-like signaling appears to increase longevity in *C. elegans* and *D. melanogaster*, whether the same is true in mammals is unclear. At least three genes ($Pit1^{dw}$, $Prop1^{dw}$, *Ghr*) have been identified in which knockout lead to dwarfism with reduced levels of IGF-1 and insulin and to increased longevity (Flurkey et al., 2001; Coschigano et al., 2000). In Snell and Ames dwarf mice, sexual maturation is delayed, and only few males are fertile, while females are invariably sterile. These mice as well as $Ghr^{-/-}$ knockout mice have significantly reduced glucose levels and fasting insulin levels, decreased tolerance to glucose and increased sensitivity to insulin which appears to be combined with reduced ability to release glucose in response to acute challenge (Bartke et al., 2003).

Recently, very strong support for the role of insulin/IGF-1 signaling pathway in the control of mammalian aging and for the involvement of this pathway in longevity of IGF-1 deficient mice was provided by Hsieh et al. (2002a,b). It was shown that in the Snell dwarf mice, GH deficiency would lead to reduced insulin secretion and alterations in insulin signaling via InRβ, IRS-1 or IRS-2 and P13K affects genes involved in the control longevity. The authors concluded that the Pit1 mutation may result in physiological homeostasis that favors longevity.

Reduction in both glucose and insulin levels as well as an increase in the sensitivity to insulin are a well-documented response to caloric restriction in rodents and monkey (Weindruch and Sohal, 1997; Mattison et al., 2003). It was shown that improved sensitivity to insulin in caloric restricted animals is specifically related to reducing visceral fat (Barzilai and Gupta, 1999). It is worthy to note that $Ghr^{-/-}$ mice have a major increase in the level of insulin receptors (Dominici et al., 2000), while Ames dwarf mice have a smaller increase in insulin receptor and substantially increased amount of insulin receptor substrates IRS-1 and IRS-2 (Dominici et al., 2002). It is worthy of note that the development of tumors in Ames dwarf mice was postponed and the incidence was reduced as compared to the control (Mattison et al., 2000; Ikeno et al., 2003).

The crucial event of the effect of caloric restriction is low levels of insulin and IGF-1 and also an increase insulin sensitivity in rodents (Chiba et al., 2002) as well as in monkeys (Mattison et al., 2003). Many characteristics of these long-lived mutants and GH receptor knockout mice resemble those of normal animals exposed to caloric restriction. These characteristics include reduced plasma levels of IGF-1, insulin and glucose, with the consequent reductions in growth and body size, delayed puberty, and significantly increased sensitivity to insulin action.

In a bid to discover whether the IGF-1 receptor might control vertebrate longevity, Holzenberger et al. (2003) inactivated the *Igf*1*r* gene by homologous recombination in mice. It was shown that $Igf1r^{-/-}$ mice dead early in the life, whereas heterozygous $Igf1r^{+/-}$ mice live on average 26% longer than their wild-type littermates ($p < 0.02$). It is worthy of note that long-lived mice do not develop dwarfism, their energy metabolism was normal. Food intake physical activity, fertility and reproduction were also unaffected in $Igf1r^{+/-}$. The spontaneous tumor incidence in the aging cohort of $Igf1r^{+/-}$ mice was similar to that in wild-type controls. It is very important that these $Igf1r^{+/-}$ mice, and mouse embryonic fibroblasts derived from them, were more resistant to oxidative stress than controls. At the molecular level, insulin receptor substrate and the *p*52 and *p*66 isoforms of *Shc*, both main substrates of IGF-1 receptor, showed decreased tyrosine phosphorylation. $p66^{Shc}$ mediated cellular responses to oxidative stress. Two main pathways—the extracellular-signal regulated kinase (ERK)/

mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)-Akt pathway—were down-regulated in $Igf1r^{+/-}$ mice.

The extension of longevity was observed in fat-specific insulin receptor knockout (FIRKO) mice (Bluher et al., 2003). These animals have reduced fat mass and were protected against age-related obesity and its subsequent metabolic abnormalities including deterioration in glucose tolerance, although their food intake was normal. Both male and female FIRKO mice were found to have an increase in mean life span (by 18%) with parallel increases in maximum life span. Extended longevity in FIRKO mice was associated with a shift in the age at which age-dependent increase in mortality risk becomes appreciable and a decreased rate of age-related mortality, especially after 36 months of age. In FIRKO mice, the resistance to obesity, despite normal food intake, suggests that metabolic rate is increased, rather than decreased (Bluher et al., 2002). The authors believe that decreased fat mass could lead to a decrease in oxidative stress in FIRKO mice. Another possibility is that the increased longevity in these mice is the direct result of altered insulin signaling.

Shimokawa et al. (2002) designed a transgenic strain of rats whose GH gene was suppressed by an anti-sense GH transgene. Male rats homozygous for the transgene (*tg*/*tg*) had a reduced number of pituitary GH cells, a lower plasma concentration of IGF-1, and a dwarf phenotype. Heterozygous rats (*tg*/−) had an intermediate phenotype in plasma IGF-1, food intake, and body weight between *tg*/*tg* and control (−/−) rats. The life span of *tg*/*tg* rats was 5–10% shorter than −/− rats. In contrast, the life span of *tg*/− rats was 7–10% longer than −/− rats. It was found that tumors caused earlier death in *tg*/*tg* rats; in contrast, *tg*/− rats had reduced non-neoplastic diseases and a prolonged life span. Immunological analysis revealed a smaller population and lower activity of splenic natural killer cells in homozygous *tg*/*tg* rats. These results provided evidence that an optimal level of the GH–IGF-1 axis function needs for longevity in mammals.

Recently it was shown that the incidence of mutations in insulin regulatory region (IRE) of APO C-III T-455 C directly correlates with longevity in humans. This is the first evidence showing that mutation located downstream to *daf*-16 in insulin signal transduction system is associated with longevity (Anisimov et al., 2001). It is worth noting that centenarians display lower degree of resistance to insulin and lower degree of oxidative stress as compared with elderly persons before 90 years (Barbieri et al., 2003). The authors suggest that centenarians may have been selected for appropriate insulin regulation as well as for the appropriate regulation of tyrosine hydroxylase (TH) gene, whose product is the rate limiting in the synthesis of catecholamines, stress-response mediators. It was shown that catecholamine may increase free radical production through induction of the metabolic rate and auto-oxidation in diabetic animals (Singal et al., 1983). Recent study on aging parameters of young (up to 39) and old (over 70) individuals having similar IGF-1 serum levels provides evidence of important role of this peptide for life potential (Ruiz-Torres and Soares de Melo Kirzner, 2002). Roth et al. (2002) analyzed data from the Baltimore Longitudinal Study of Aging and reported that survival was greater in men who maintained lower insulin level.

3. Effect of antidiabetic biguanides on insulin/IGF-1 signaling pathway and longevity

Several years ago, it was suggested to use biguanide antidiabetics as a potential anti-aging treatment (Dilman, 1971). The antidiabetic drugs, phenformin (1-phenylethyl-biguanide), buformin (1-butylbiguanide hydrochloride) and metformin (*N*,*N*-dimethylbiguanide) were observed to reduce hyperglycemia, improve glucose utilization, reduce free fatty acid utilization, gluconeogenesis, serum lipids, insulin, somatomedin, reduce body weight and decrease metabolic immunodepression both in humans and rodents (Muntoni, 1999; Dilman, 1994; Berstein et al., 1992). Nowadays, phenformin is not used in clinical practice due to it side effects (mainly lactic acidosis) observed in patients with non-compensated diabetes. It is worthy of note that during more than 10-year-long experience of administration of phenformin to patients without advanced diabetes Dilman (1994) observed no cases of lactic acidosis or any other side effects. Nevertheless, we believe that the analysis of results of long-term administration of this drug as well as another antidiabetic biguanides (buformin and metformin) to non-diabetic animals is seems very important for understanding of links between insulin and longevity.

Buformin was supplemented to nutrient medium in various concentration (from 1.0 to 0.00001 mg/ml) during the larvae stage and over the life span of *C. elegans*. The drug given at the concentration of 0.1 mg/ml increased the mean life span of the nematoda by 23.4% ($p < 0.05$) and the maximum life span by 26.1% as compared to the controls (Bakaev, 2002).

The available data on effect of antidiabetic biguanides on life span in mice and rats summarized in Table 1. The treatment with phenformin prolonged the mean life span of female C_3H/Sn mice by 21% ($p < 0.05$), the mean life span of last 10% survivors by 28% and the maximum life span by 5.5 months (by 26%) in comparison with the control. At the time of death of the last mice in the control group 42% of phenformin-treated mice were alive (Fig. 1; Dilman and Anisimov, 1980).

Administration of phenformin increased the mean life span of the last 10% survivors by 10% ($p < 0.005$), and maximum life span by 3 months (+10%) in comparison with the controls (Table 1). The treatment with phenformin slightly decreased the body weight of rats in comparison with the control ($p > 0.05$). The disturbances in the estrus function observed in 36% of 15–16-month old rats of

Table 1
Effect of antidiabetic biguanides on mortality rate in mice and rats

Species, strain	Treatment	No. of animals	Life span (days)			Reference
			Mean	Last 10% of survivors	Maximum	
C_3H/Sn mice	Control	30	450 ± 23.4	631 ± 11.4	643	Dilman and Anisimov (1980)
	Phenformin	24	545 ± 39.2 (+21.1%)	810 ± 0** (+28.4%)	810 (+26%)	
LIO rats	Control	41	652 ± 27.3	885 ± 11.3	919	Anisimov (1982)
	Phenformin	44	652 ± 28.7	974 ± 16.2** (+10.1%)	1009 (+9.8%)	
	Control	74	687 ± 19.2	925 ± 22.5	1054	Anisimov (1980)
	Buformin	42	737 ± 26.4 (+7.3%)	1036 ± 38.9* (+12%)	1112 (+5.5%)	

The difference with control is significant: *$p < 0.05$; **$p < 0.01$ (Student's t-test).

the control group and only in 7% of rats in phenformin-treated group ($p < 0.05$) (Anisimov, 1982, 1987).

The treatment with buformin slightly increased mean life span of rats (by 7%; $p > 0.05$). The mean life span of the last 10% survivors increased by 12% ($p < 0.05$) and the maximum life span increased by 2 months (+5.5%) as compared with controls. The body weight of rats treated with buformin was slightly (5.2–9.4%) but statistically significantly ($p < 0.05$) decreased in comparison with the control from the age of 12–20 months ($p < 0.05$). At the age of 16–18 months 38% of control rats revealed the disturbances in the estrus cycle, whereas in females treated with buformin these disturbances were observed only in 9% of rats ($p < 0.05$) (Anisimov, 1980). Recently it was found that metformin, like buformin and phenformin, significantly increases the life span of rats (Roth, personal communication).

Several other effects of treatment with antidiabetic biguanides related to reproduction and aging, are known from earlier studies. For example, it decreased hypothalamic threshold of the sensitivity to feedback inhibition by estrogens (Dilman and Anisimov, 1979a), which is one of the most important mechanisms regulating age-related decline and switch-off of the reproductive function (Dilman and Anisimov, 1979a; Rossmanith, 2001; Hung et al., 2003). It is worthy of note that another antidiabetic biguanide, metformin, may improve menstrual regularity, leading to spontaneous ovulation, and enhance the induction of ovulation with clomiphene citrate in women with polycystic ovary syndrome (Awartani and Cheung, 2002). The treatment with phenformin also decreased hypothalamic threshold sensitivity to feedback regulation by glucocorticoids and by metabolic stimuli (glucose and insulin) (Dilman, 1994). It was recently shown that elements involved in the insulin/IGF-1 signaling pathway are regulated at the expression and/or functional level in the central nervous system. This regulation may play a role in the brain's insulin resistance (Fernandes et al., 2001), in the control of ovarian follicular development and ovulation (Richards et al., 2002), and brain's control of life

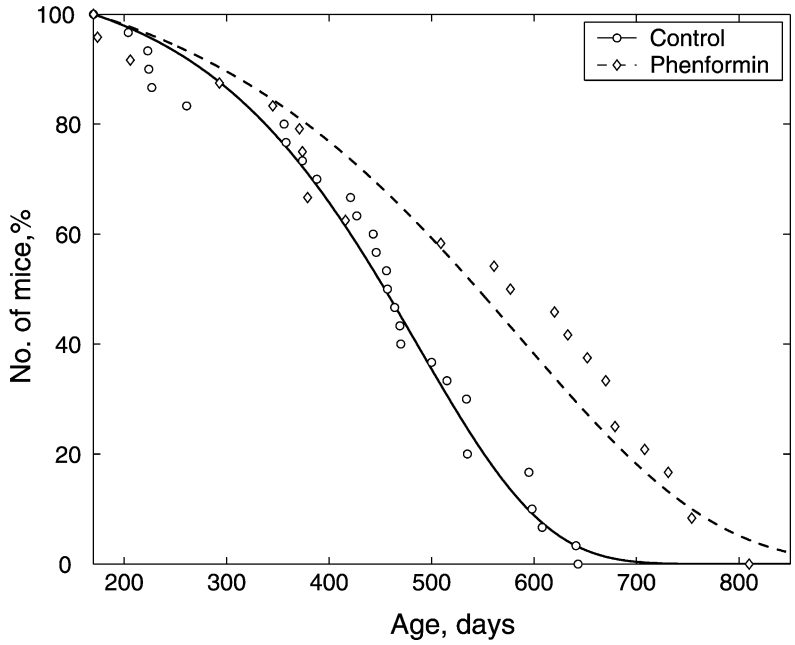

Fig. 1. Effect of phenformin on the survival in female C_3H/Sn mice.

Table 2
Effect antidiabetic biguanides on carcinogenesis in mice and rats

Species	Drug	Main target(s)	Carcinogen	Effect of treatment	Reference
Mouse	Phenformin	Mammary gland	Spontaneous	Inhibition	Dilman and Anisimov (1980)
	Phenformin	Subcutaneous tissue	MCA	Inhibition	Vinnitski and Iakimenko (1981)
Rat	Buformin	Total incidence	Spontaneous	Inhibition	Anisimov (1980)
	Phenformin	Total incidence	Spontaneous	Inhibition	Anisimov (1982)
	Phenformin	Mammary gland	DMBA	Inhibition	Dilman et al. (1978)
	Phenformin	Mammary gland	NMU	Inhibition	Anisimov et al. (1980a)
	Buformin	Mammary gland	DMBA	Inhibition	Anisimov et al. (1980b)
	Buformin	Nervous system	NMU, transplacentally	Inhibition	Alexandrov et al. (1980)
	Phenformin	Nervous system, kidney	NEU, transplacentally	Inhibition	Bespalov and Alexandrov (1985)
	Phenformin	Colon	DMH	Inhibition	Dilman et al. (1977)
	Phenformin	Total incidence	X-rays	Inhibition	Anisimov et al. (1982)
Hamster	Metformin	Pancreas	NBOPA	Inhibition	Schneider et al. (2001)

Abbreviations: DMH, 1,2-dimethylhydrazine; MCA, 20-methylcholanthrene; NBOPA, *N*-nitrosobis-(2-oxopropyl)amine; NEU, *N*-nitrosoethylurea; NMU, *N*-nitrosomethylurea; X-rays, total-body X-ray irradiation.

span (Chiba et al., 2002; Mattson et al., 2002). Antidiabetic biguanides also alleviated age-related metabolic immunodepression (Dilman, 1994). These mechanisms can be involved in geroprotective effect of biguanides. Treatment with chromium picolinate, which elevated the insulin sensitivity in several tissues, including hypothalamus, significantly increased the mean life span and decreased the development of age-related pathology in rats (McCarty, 1994). We hypothesized that antidiabetic biguanides and possibly chromium picolinate, have regulate thyrosine hydroxylase and insulin/IGF-1 signaling pathway genes both associated with longevity (De Benedictis et al., 2001; Kenyon, 2001). It was shown that the polymorphism at TH-INS locus affects non-insulin dependent type 2 diabetes (Huxtable et al., 2000), and is associated with hypothalamic obesity (Weaver et al., 1992), polycystosis ovary syndrome (Waterworth et al., 1997), hypertriglyceridemia and atherosclerosis (Tybaierg-Hansen et al., 1990).

4. Effect of antidiabetic biguanide on carcinogenesis

Long-term treatment with phenformin significantly inhibited the incidence of spontaneous mammary tumors in female C_3H/Sn mice (Fig. 2) and in female rats (Dilman and Anisimov, 1980; Anisimov, 1982) whereas total tumor incidence was decreased by 49.5% in buformin-treated rats (Anisimov, 1980).

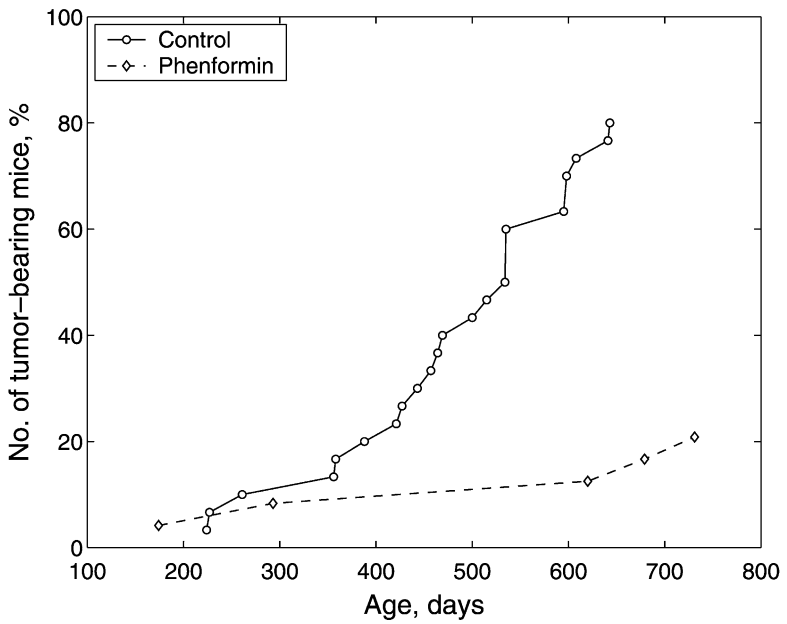

Fig. 2. Effect of phenformin on tumor yield curve in female C_3H/Sn mice.

The anticarcinogenic effect of antidiabetic biguanides has been demonstrated in several models of induced carcinogenesis (Table 2). The treatment with phenformin normalized the tolerance to glucose and serum insulin and IGF-1 level in rats exposed to intravenous injections of *N*-nitrosomethylurea (NMU) and inhibited mammary carcinogenesis in these animals (Anisimov et al., 1980a). Treatment of rats with 1,2-dimethylhydrazine (DMH) caused the decrease in the level of biogenic amines, particularly, of dopamine in the hypothalamus, the decrease of glucose tolerance and the increase of the blood level of insulin and triglycerides. Administration of phenformin restored immunological indices and inhibited DMH-induced colon carcinogenesis (Dilman et al., 1977; Anisimov et al., 1980c). It is worthy to note that colon 38 adenocarcinoma growth was significantly inhibited in liver-specific IGF-1-deficient mice whereas injections with recombinant human IGF-1 displayed sufficiently promoted the tumor growth and metastasing (Wu et al., 2002).

A decrease of glucose utilization was found in the 3-month-old female progeny of rats exposed to NMU on the 21st day of pregnancy (Alexandrov et al., 1980). Postnatal treatment with biguanides started from the age of 2 months significantly inhibited the development of malignant neurogenic tumors in rats transplacentally exposed to NMU or NEU (Alexandrov et al., 1980; Bespalov and Alexandrov, 1985; Table 2). In high fat-fed hamsters, the treatment with *N*-nitrosobis-(2-oxopropyl)amine was followed by the development of pancreatic malignancies in 50% of cases, whereas no tumors were found in the hamsters treated with the carcinogen and metformin (Schneider et al., 2001).

Thus, anticarcinogenic effect of antidiabetic biguanides has been demonstrated in relation to spontaneous carcinogenesis in mice and rats, in different models of chemical carcinogenesis in mice, rats and hamsters, and in radiation carcinogenesis model in rats. Phenformin administered orally to rodents potentiated the antitumor effect of cytostatic drugs on transplantable tumors (Dilman and Anisimov, 1979b).

The comparative study of 10-years results of metabolic rehabilitation (included restricted in fat and carbohydrate diet and treatment with antidiabetic biguanides) of cancer patients had shown significant increase in the survival of breast and colorectal cancer patients, the increase in the length of cancer-free period, the decrease in the incidence of metastasis as compared with control patients (Berstein et al., 1992).

Although it is known that free radicals are produced during metabolic reactions, it is largely unknown which factor(s), of physiological or pathophysiological significance, modulate their production in vivo. It has been suggested that hyperinsulinemia may have increase free radicals and therefore promote aging, independent of glycemia (Dilman, 1971, 1994; Facchini et al., 2000a, 2001). Plasma levels of lipid hydroperoxides are higher, and antioxidant vitamins are lower in individuals who are resistant to insulin-stimulated glucose disposal but otherwise glucose tolerant, nonobese, and normotensive (Facchini et al., 2000b). There is substantial evidence supporting the hypothesis that selective resistance to insulin-stimulated (muscle) glucose disposal and the consequential compensatory hyperinsulinemia trigger a variety of metabolic effects, likely resulting in accelerated oxidative stress and aging (Dilman, 1994; Facchini et al., 2000a).

The antidiabetics biguanides inhibit fatty acid oxidation, inhibit gluconeogenesis in the liver, increase the availability of insulin receptors, inhibit monoamine oxidase (Muntoni, 1999), increase sensitivity of hypothalamo-pituitary complex to negative feedback inhibition, reduce excretion of

Table 3
Comparison of characteristics of rodents subjected to normal aging, caloric restriction, genetic modifications or treatment with antidiabetic biguanides

Parameters	Aging	Calorie restriction	Dwarf mice	GHR$^{-/-}$	Igf1r$^{+/-}$	FIRKO	Biguanides
Life span extension	↓	+40–50%	+50%	+46%	+33%	+18%	+20%
Tolerance to glucose	↓	↑	↓	↓	↑ ↓[a]	= or ↑	↑
Sensitivity to insulin	↓	↑	↑	↑	↑	↑ in fat	↑
Serum level							
Insulin	↑	↓	↓	↓	=	↓	↓
GH	↓	↓	Absent	↑	ND	↓	↓
IGF-1	↓	↓	↓	↓	↓	↓	↓
Body size	↑	↓	↓	↓	↓	↓	↓
Body fat content	↑	↓	↑	ND	↑ ↓	↓	↓
Reproductive function	↓	↓[b]	↓[b]	↓[b]	=[b]	ND	↑
Thyroid function	↓	↓	↓	↓	=	ND	↑
Serum corticosterone	↑	↑	=	=	ND	ND	↓
Immune function	↓	↓	= or ↓	ND	ND	ND	↑
Resistance to oxidative stress	↓	↑	↓	↓	↑	↑	↑
Tumor incidence	↑	↓	= or ↓	=	=	ND	↓

Note: ↓, decrease; ↑, increase; =, no effect; ND, no available data.
[a] The tolerance to glucose is increased in females but decreased in male.
[b] Reproductive function in relation to normal aging mice.

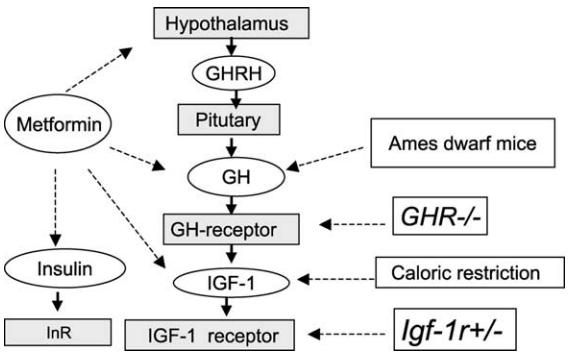

Fig. 3. Proposed effects of metformin, caloric restriction and genetic modifications on insulin/IGF-1 signaling pathway in the control of aging.

glucocorticoid metabolites and dehydroepiandrosterone-sulfate (Dilman, 1994). These drugs have been proposed for the prevention of the age-related increase of cancer and atherosclerosis, and for retardation of the aging process (Dilman, 1971, 1994). It has been shown that administration of antidiabetic biguanides into patients with hyperlipidemia lowers the level of blood cholesterol, triglycerides, and β-lipoproteins. It also inhibits the development of atherosclerosis, reduces hyperinsulinemia in men with coronary artery disease. It increases hypothalamo-pituitary sensitivity to inhibition by dexamethasone and estrogens, causes restoration of estrous cycle in persistent-estrous old rats, improves cellular immunity in atherosclerotic and cancer patients, lowers blood IGF-1 levels in cancer and atherosclerotic patients with Type IIb hyperlipoproteinemia, (Dilman, 1994). Recently it was shown that metformin decreases platelet superoxide anion production in diabetic patients (Gargiulo et al., 2002).

5. Conclusion

The striking similarities have been described between insulin/IGF-1 signaling pathways in yeast, worms, flies, and mice (Kenyon, 2001). Many characteristics of mice that are long-lived due to genetic modifications resemble effects of caloric restriction in wild-type (normal) animals (Table 3). Comparison of characteristics of exposed to these endogenous and exogenous influences shows a number of similarities but also some differences (Fig. 3). Effects of antidiabetic biguanides seems to be more adequate in the prevention of age-related deteriorations in glucose metabolism and in insulin signaling pathway as well as in such important for longevity parameters as a fertility and a resistance to oxidative stress and tumorigenesis than those induced by caloric restriction and genetic manipulations.

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