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Effects of interventions on adiponectin and adiponectin receptors

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Adiponectin secreted from adipose tissue binds to two distinct adiponectin receptors (AdipoR1 and AdipoR2) identified and exerts its anti-diabetic effects in insulin-sensitive organs including liver, skeletal muscle and adipose tissue as well as amelioration of vascular dysfunction in the various vasculatures. A number of experimental and clinical observations have demonstrated that circulating levels of adiponectin are markedly reduced in obesity, type 2 diabetes, hypertension, and coronary artery disease. Therapeutic interventions which can improve the action of adiponectin including elevation of circulating adiponectin concentration or up-regulation and/or activation of its receptors, could provide better understanding of strategies to ameliorate metabolic disorders and vascular disease. The focus of the present review is to summarize accumulating evidence showing the role of interventions such as pharmacological agents, exercise, and calorie restriction in the expression of adiponectin and adiponectin receptors.

Keywords: Pharmacological agents, Exercise, Calorie restriction, Adiponectin, Adiponectin receptors

INTRODUCTION

Nutrition imbalance and physical inactivity due to sedentary life style can lead to obesity, which is closely associated with an increased risk of metabolic syndrome (Booth et al., 2011; Booth et al., 2012). Metabolic disorders including insulin resistance and overt type 2 diabetes (T2D) are highly related to secondary cardiovascular complications such as hypertension, myocardial infarction, and stroke (Abate, 2000; Meshkani and Adeli, 2009). Adiponectin is one of adipokines secreted from adipose tissue and involved in various biological processes such as energy homeostasis, immune actions, and vascular homeostasis (Cheng et al., 2014; Hui et al., 2012). A number of clinical observations have demonstrated that circulating levels of adiponectin are markedly reduced in patients with obesity (Arita et al., 1999), T2D (Hotta et al., 2000), essential hypertension (Adamczak et al., 2003), and coronary artery disease (CAD) (Kumada et al., 2003; Nakamura et al., 2004). Based on above considerations, therapeutic interventions which can improve the action of adiponectin including elevation of circulating adiponectin concentration or up-regulation and/or activation of its receptors, could provide better understanding of strategies to ameliorate metabolic disorders and vascular disease. The focus of the present review is to summarize accumulating evidence showing the role of interventions such as pharmacological agents, exercise, calorie restriction (CR), and gastric bypass surgery (weight loss) in the expression of adiponectin and adiponectin receptors.

EFFECTS OF INTERVENTIONS ON ADIPONECTIN AND ADIPONECTIN RECEPTORS

Pharmacological/dietary interventions and lifestyle modifications such as exercise and CR to prevent and ameliorate cardiovascular disease and micro-vascular complications in T2D, have been shown to increase circulating levels of adiponectin in both experimental models and human studies (Simpson and Singh, 2008; Zhu et al., 2008). Up-regulation of endogenous adiponectin and

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its receptors by interventions might have multiple beneficial effects on metabolic and cardiovascular diseases.

Pharmacological and dietary intervention

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor superfamily which functions as transcription factors regulating gene expression and play important roles in the regulation of cellular differentiation, development, and energy metabolism (Schoonjans et al., 1996). The three types of PPAR (α, γ, and β/δ) have been identified (Schoonjans et al., 1996). The PPAR-γ agonists, thiazolidinediones (TZDs) are widely used for anti-diabetic drugs that improve insulin sensitivity through enhancement of glucose disposal as well as reduction of gluconeogenesis in the target tissues of the body including skeletal muscle, liver, and adipose tissue (Furnsinn and Waldhausl, 2002; Kintscher and Law, 2005). A number of studies have shown that TZDs such as rosiglitazone and pioglitazone increased circulating levels of adiponectin in both human and experimental rodent models (Choi et al., 2005; Iwaki et al., 2003; Kubota et al., 2006; Pajvani et al., 2004). In addition to PPAR-γ, the PPAR-α agonist induced the increase in the circulating level of adiponectin associated with improvement in insulin sensitivity. For example, fenofibrate an agonist of nuclear receptor PPAR-α, increased serum levels of adiponectin in patients with primary hypertriglyceridemia (Koh et al., 2005). Previous studies have implicated that hypoadiponectinemia is associated with hypertension (Adamczak et al., 2003; Papadopoulos et al., 2009). Therefore, it is tempting to speculate whether anti-hypertensive drugs such as candesartan and losartan (angiotensin II receptor antagonists) increase adiponectin. These drugs, indeed, elevated circulating adiponectin without altering adiposity (Celik et al., 2006; Furuhashi et al., 2003; Koh et al., 2004; Koh et al., 2006). In addition, several other drugs for anti-diabetic (glimepiride) and anti-hypertension (nebivolol, β_1 receptor blocker) have been shown to enhance plasma adiponectin concentrations in human subjects (Celik et al., 2006; Nagasaka et al., 2003). However, it is unclear whether elevated adiponectin is associated with improved cardiovascular outcomes.

In addition to pharmacological agents, dietary fish oils (FO) and polyunsaturated fatty acids (PUFA) have been shown to increase mRNA expression of adiponectin in adipose tissue and circulating levels of adiponectin in several experimental models and human (Mostowik et al., 2013; Neschen et al., 2006; Rossi et al., 2005). Furthermore, Oolong tea, green tea extract and (-)-catechin increased plasma adiponectin in humans and rodent models (Cho et al., 2007; Li et al., 2006; Shimada et al., 2004). Table 1 summarized the effects of pharmacological agents and dietary intervention on the expression of adiponectin.

Exercise

It is well documented that exercise or regular physical activity has beneficial effects on metabolic and cardiovascular disease. Considering previous literatures, it is unclear whether exercise training (physical activity) increases adiponectin in circulation and its receptors in insulin-sensitive tissues such as adipose tissue, liver, and skeletal muscle. Complicating interpretation of the existing data is dependent on multiple factors including species, the pathological condition, types (endurance vs resistance exercise), intensity (low, moderate, and intense), and duration of exercise (acute vs chronic, short-term vs long-term), and sex. For example, in healthy, young subjects, it seemed that both acute and chronic aerobic exercise did not alter plasma level of adiponectin (Ferguson et al., 2004; Hulver et al., 2002; Jurimae et al., 2006; Punyadeera et al., 2005). However, chronic endurance training increased plasma adiponectin in obese adolescents (Balagopal et al., 2005), obese adults (Kondo et al., 2006), Caucasian subjects with impaired glucose tolerance (IGT) and T2D (Bluher et al., 2006; Oberbach et al., 2006). Furthermore, endurance training increased mRNA expression of adiponectin receptor (AdipoR) 1 and 2 in adipose tissue and skeletal muscle in normal glucose tolerance (NGT), IGT, and type 2 diabetic patients (Bluher et al., 2006; Bluher et al., 2007; Oberbach et al., 2006). On the other hand, some studies by several other groups have shown that aerobic exercise did not change adiponectin expression in obese subject (Polak et al., 2006), insulin resistant female subjects (Marcell et al., 2005), and patients with T2D (Boudou et al., 2003; Yokoyama et al., 2004). Interestingly, Fatouros et al. have demonstrated that only moderate-high intensity resistance training, not low intensity, increased plasma adiponectin in inactive subjects, suggesting that the intensity of exercise may be an important factor in the expression of adiponectin (Fatouros et al., 2005). Table 2 shows a summary of studies examining effects of exercise training on adiponectin and AdipoRs in both human and experimental models.

Calorie restriction, weight loss, and gastric bypass surgery

Calorie restriction (CR) refers to a dietary regimen low in calories without malnutrition and is known as an efficient lifestyle modification that delays the onset of metabolic and cardiovascular disease (Cava and Fontana, 2013). Weight loss and/or CR have been shown to improve insulin resistance, T2D, and cardiovascular dysfunction in both human and rodent models (Weiss and

Table 1. Effects of pharmacological agents and dietary intervention on adiponectin

Subject or animal	Sex	Pharmacological agents	Duration	Methods for intake	Tissues	Methods	Conclusions	References
Non-diabetic patients	Female	-Pioglitazone (1-3 μM)	24 h	Cell culture	Subcutaneous fat (Biopsy)	PCR WB	= APN ↑ HMW APN	Bodles et al., 2006
Normal volunteers	Male	-Rosiglitazone (4 mg twice/daily)	2 wk	Oral intake	Serum	Velocity sedimentation	↑ Total APN ↑ HMW APN	Pajvani et al., 2004
Healthy normal weight subjects	Both	-Flaxseed oil (15 mL/day) -Olive oil (15 mL/day)	6 wk	Oral intake	Plasma	ELISA	= APN = APN	Kontogianni et al., 2013
Patients with primary hypertriglyceridemia	Both	-Fenofibrate (200 mg daily)	8 wk	Oral intake	Serum	ELISA	↑ APN	Koh et al., 2005
Patients with hypercholesterolemic hypertension	Both	-Simvastatin (20 mg) +Losartan (100 mg) -Losartan only (100 mg/daily)	2 mo	Oral intake	Plasma	ELISA	↑ APN ↑ APN	Koh et al., 2004
Patients with essential hypertension	Both	-Temocapril (4 mg/daily) -Candesartan (8 mg/daily)	2 wk	Oral intake	Serum	ELISA	↑ APN ↑ APN	Furuhashi et al., 2003
Patients with mild to moderate hypertension	Both	-Candesartan (16 mg/daily)	2 mo	Oral intake	Plasma	ELISA	↑ APN	Koh et al., 2006
Patients with hypertension	Both	-Nebivolol (5 mg/daily) -Metoprolol (100 mg/daily)	6 mo	Oral intake	Plasma	ELISA	↑ APN = APN	Celik et al., 2006
Patients with T2D	Both	-Glimepiride (1.9 mg/daily) -Metformin (750 mg/daily)	3 mo	Oral intake	Serum	ELISA	↑ APN ↑ APN	Nagasaka et al., 2003
Patients with CAD	Both	-Oolong tea (1,000 mL) vs. water	1 mo	Oral intake	Plasma	ELISA	↑ APN	Shimada et al., 2004
Patients with CAD	Both	-Omega-3 PUFA	4 wk	Oral intake	Plasma	ELISA	↑ APN	Mostowik et al., 2013
Rats (OLETF)	Male	-Rosiglitazone (2 mg/kg/day) -Fenofibrate (100 mg/kg/day)	40 wk	In food	Serum	ELISA	↑ APN = APN	Choi et al., 2005
Rats (Wistar)	Male	-Sucrose Rich Diet -Sucrose Rich Diet (7 mo)+FO Diet (2 mo)	9 mo	In food	Plasma	ELISA	↓ APN ↑ APN	Rossi et al., 2005
Hamsters (Golden Syrian)	Male	-Green tea extract (low dose 150 mg/kg) -Green tea extract (high dose 300 mg/kg)	4 wk	Oral gavage	Plasma	ELISA	↑ APN ↑ APN	Li et al., 2006
Hamsters (Golden Syrian)	Male	-Niacin (1,200 mg/kg)	18 days	Oral gavage	AT	PCR	↑ APN	Connolly et al., 2013
Mice (ob/ob)	Male	-Pioglitazone (10 mg/kg) -Pioglitazone (30 mg/kg)	2 wk	Oral gavage	Serum	ELISA	↑ APN ↑↑ APN	Kubota et al., 2006
Mice (db/db)	Male	-Troglitazone (0.2%) -Pioglitazone (0.01%)	2 wk	In food	Subcutaneous AT Serum	PCR WB	↑ APN ↑ APN	Iwaki et al., 2003
Mice (db/db)	Male	-Rosiglitazone (10 mg/kg)	11 days	Oral gavage	Serum	Velocity sedimentation	= Total APN ↑ HMW APN	Pajvani et al., 2004
Mice (129 Sv)	Male	-27% Fish oil	8 or 15 days	In food	Plasma Epididymal AT Subcutaneous AT	ELISA PCR PCR	↑ APN ↑ APN = APN	Neschen et al., 2006
Mice (3T3-L1 adipocytes)	-	(-)-catechin (50 μM) (-)-catechin (5-100 μM) (-)-catechin (50 μM)	24 h	Cell culture	Adipocytes	WB ELISA PCR	↑ APN ↑ APN ↑ APN	Cho et al., 2007

APN, adiponectin; AT, adipose tissue; CAD, coronary artery disease; db/db, leptin receptor mutated mouse; ELISA, enzyme linked immunosorbent assay; FO, fish oil; HMW, high molecular weight; OLETF rat, Otsuka Long-Evans Tokushima fatty rat; ob/ob, leptin deficient mouse; PCR, polymerase chain reaction; PUFA, polyunsaturated fatty acid; T2D, type 2 diabetes; WB, western blotting; ↑, increase; ↓, decrease; =, no change.

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Table 2. Effects of exercise on adiponectin and adiponectin receptors

Subject or animal	Sex	Type of exercise	Duration	Tissues	Methods	Conclusions	References
Healthy subjects	Both	Cycle ergometry training	60 min (Acute)	Plasma	ELISA	= APN	Ferguson et al., 2004
Healthy subjects	Both	Aerobic training	6 mo (4 days/wk)	Plasma	ELISA	= APN	Hulver et al., 2002
Healthy non-obese subjects	Male	Ergometer training	6 wk (5 days/wk)	Serum	ELISA	↓ APN (At 16 h after the last training session)	Yatagai et al., 2003
Young subjects	Male	Cycle ergometer	2 h (Acute)	Plasma	ELISA	= APN	Punyadeera et al., 2005
Highly-trained young rowers	Male	Rowing ergometer	Maximal 6,000 m test (Acute)	Plasma	ELISA	↑ APN (After 30 min of recovery)	Jurimae et al., 2005
Highly-trained young rowers	Male	Training for rowers	6 mo	Plasma	ELISA	= APN	Jurimae et al., 2006
Inactive subjects	Male	Resistance training (low, moderate, high intensity)	6 mo (3 days/wk)	Plasma	ELISA	= APN (low intensity) ↑ APN (moderate) ↑ APN (high)	Fatouros et al., 2005
Young overweight subjects	Male	Cycle ergometer	45 min (Acute)	Plasma	ELISA	= APN (Post 24, 48 h)	Jamurtas et al., 2006
Obese subjects	Both	Aerobic exercise + hypo-caloric (ExHypo) or eucoloric (ExEu) diet	12 wk (5 days/wk)	Serum Skeletal muscle	ELISA PCR	↑ HMW/Total APN ↑ AdipoR1 and 2	O'Leary et al., 2007
Obese subjects	Female	Aerobic exercise (Bicycle ergometer)	12 wk (5 days/wk)	Plasma SCAAT (biopsy)	ELISA PCR	= APN = APN	Polak et al., 2006
Obese subjects	Female	Endurance training	7 mo (4-5 days/wk)	Plasma	ELISA	↑ APN	Kondo et al., 2006
Obese adolescents	Both	Aerobic activities	3 mo (3 days/wk)	Plasma	ELISA	↑ APN	Balagopal et al., 2005
Middle-aged subjects with insulin resistance	Both	Aerobic exercise (moderate to intense)	16 wk (5 days/wk)	Plasma	ELISA	= APN	Marcell et al., 2005
Caucasian subjects with NGT, IGT, and T2D	Both	Physical training	4 wk (3 days/wk)	Serum Skeletal muscle	ELISA PCR	↑ APN ↑ AdipoR1 and 2	Bluher et al., 2006
Caucasian subjects with NGT, IGT, and T2D	Both	Physical training	4wk (3 days/wk)	Subcutaneous AT Skeletal muscle	PCR PCR	↑ AdipoR1 and 2 ↑ AdipoR1 and 2	Bluher et al., 2007
Caucasian subjects with NGT, IGT, and T2D	Both	Physical training program (Aerobic + Power training)	4 wk (3 days/wk)	Plasma	ELISA	= APN in NGT ↑ APN in IGT ↑ APN in T2D	Oberbach et al., 2006
Caucasian subjects with NGT, IGT, and T2D	Both	Physical training (Aerobic exercise)	4 wk (3 days/wk)	Plasma Skeletal muscle	ELISA PCR	↑ APN in NGT, IGT and T2D ↑ AdipoR1 and 2 in NGT, IGT, and T2D	Bluher et al., 2006
Patients with T2D	Both	Aerobic exercise (walking and bicycle ergometer)	3 wk (5 days/wk)	Plasma	ELISA	= APN	Yokoyama et al., 2004
Middle-aged subjects with T2D	Male	Endurance training	8 wk (3 days/wk)	Plasma	ELISA	= APN	Boudou et al., 2003
Older, healthy subjects	Both	Aerobic and resistance exercise training	12 wk (3 days/wk)	Serum	ELISA	↑ APN	Markofski et al., 2013
Rats (SD)	Male	Endurance training	6 mo (5 days/wk)	Serum Skeletal muscle Adipose Skeletal muscle Adipose	ELISA PCR PCR WB WB	↑ APN ↑ APN = APN ↑ APN ↑ APN	Dai et al., 2013
Mice (Swiss)	Male	Swimming exercise	12 wk (5 days/wk)	Adipose Liver Skeletal muscle	WB	↑ AdipoR1 ↑ AdipoR1 ↑ AdipoR1	Farias et al., 2012
Mice (db/db)	Male	Endurance training	10 wk (5 days/wk)	Serum	ELISA	↑ APN	Lee et al., 2011
Mice (KKAy)	Male	Endurance training	8 wk (5 days/wk)	Skeletal muscle Skeletal muscle Liver Liver White adipose White adipose	PCR	↑ AdipoR1 = AdipoR2 ↑ AdipoR1 ↓ AdipoR1 = AdipoR1 = AdipoR1	Huang et al., 2006
Mice (C57BL/6)	Male	Voluntary wheel running	6 wk	Plasma	ELISA	= APN	Bradley et al., 2008

AdipoR, adiponectin receptor; APN, adiponectin; AT, adipose tissue; SCAAT, subcutaneous abdominal adipose tissue; db/db, leptin receptor mutated mouse; ELISA, enzyme linked immunosorbent assay; HMW, high molecular weight; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PCR, polymerase chain reaction; SD, Sprague Dawley; T2D, type 2 diabetes; WB, western blotting; ↑, increase; ↓, decrease; =, no change.

Table 3. Effects of calorie restriction (CR), weight loss, and gastric bypass surgery on adiponectin

Subject or animal	Sex	Type of treatment	Duration	Tissues	Methods	Conclusions	References
Normal subjects	Both	CR	≤7 yr	Serum	ELISA	↑ APN	Fontana et al., 2010
Normal weight subjects	Female	CR (1,000-1,200 kcal/day)	4 wk	Plasma	ELISA	↓ APN	Wolfe et al., 2004
Caucasian subjects	Male	CR (low calorie diet, 800 kcal/day)	12 wk	Serum	ELISA	↑ APN	Schulte et al., 2013
Obese subjects	Both	CR program	3 mo	Plasma	ELISA	↑ HMW APN ↓ hexamer APN ↓ trimer APN	Kobayashi et al., 2004
Obese subjects	Female	CR (↓ 600 kcal/day)	5-6 mo	Adipose Adipose Plasma Adipose Adipose Adipose	PCR ELISA ELISA WB WB WB	↑ APN ↑ APN = Total APN ↑ HMW APN = MMW APN ↓ LMW APN	Rossmeislova et al., 2013
Obese subjects	Both	CR (weight loss, very low caloric diet)	12 wk	Serum	ELISA	↑ APN	Oberhauser et al., 2012
Obese subjects	Female	CR (very low calorie diet)	3 wk	Serum	ELISA	= APN	Anderlova et al., 2006
Severely obese subjects	Female	CR (low-calorie diet, less than 5% weight loss or 5-10% weight loss)	3 wk	Plasma	ELISA	= APN (less than 5%) ↑ APN (5-10% weight loss)	Varady et al., 2009
Obese subjects with metabolic syndrome	Both	CR (very low-calorie diet)	12 mo	Plasma	ELISA	= APN	Xydakis et al., 2004
Patients with T2D	Both	Low calorie diet Roux-en-Y gastric bypass	3 mo	Plasma	ELISA	= APN ↑ APN	Plum et al., 2011
Rats (F344/NSlc)	Male	CR	4 wk	Plasma	ELISA	= HMW APN	Plum et al., 2011
Rats (SD)	Male	CR (40%)	6 mo	Serum Skeletal muscle Adipose Skeletal muscle Adipose	ELISA PCR PCR WB WB	↑ APN ↑ APN ↑ APN ↑ APN ↑ APN	Dai et al., 2013
Rats (SD)	Male	CR (40%)	26 wk	Serum	ELISA	↑ APN	Cerqueira et al., 2012
Rats (SHRs)	Male	CR	5 wk	Plasma	ELISA	↑ APN	Cerqueira et al., 2012
Mice (C57BL/6)	Female	CR	8 wk	Serum	ELISA	↑ APN	Wheatley et al., 2011
Mice (C57BL/6N)	Female	CR (30% caloric-restricted diet)	10 wk	Serum	ELISA	↑ APN	Fenton et al., 2009
Mice (C57BL/6J)	Female	CR Alternate-day fasting	4 wk	Plasma	ELISA	↑ APN ↑ APN	Varady et al., 2010
Mice (C57BL/6)	Male	CR	8 wk	Plasma	ELISA	↑ APN	Wang et al., 2007

APN, adiponectin; CR, calorie restriction; ELISA, enzyme linked immunosorbent assay; HMW, high molecular weight; LMW, low molecular weight; MMW, medium molecular weight; PCR, polymerase chain reaction; SD, Sprague Dawley; T2D, type 2 diabetes; SHRs, spontaneously hypertensive rats; WB, western blotting; ↑, increase; ↓, decrease; =, no change.

Fontana, 2011). In addition, sustained weight loss by gastric bypass surgery ameliorated cardiovascular dysfunction (Brethauer et al., 2011; Zhang et al., 2011). Although it is not clear whether beneficial effects of these interventions are mediated by adiponectin signaling pathways, a number of studies have shown that CR and/or weight loss by gastric bypass surgery increased circulating levels of adiponectin. For example, CR increased circulating adiponectin in normal (Fontana et al., 2010; Schulte et al., 2013) and obese subjects (Kobayashi et al., 2004; Oberhauser et al., 2012; Varady et al., 2010). However, some studies have shown that CR did not change plasma levels of adiponectin in patients with metabolic syndrome (Xydakis et al., 2004) and T2D (Plum et al., 2011). Interestingly, Varady et al. (2009) have implicated that circulating adiponectin concentration increased 20% in the 5-10% weight loss group, not less than 5% weight loss group, suggesting a minimum degree of weight loss are required to improve adipokine profile in severely obese women. On the other hand, Plum et al. suggested that Roux-en-Y gastric bypass sur-

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gery, not low calorie diet group, increased plasma adiponectin concentration in patients with T2D, although weight loss was comparable in both groups (Plum et al., 2011). This may suggest that Roux-en-Y gastric bypass surgery is more effective method than low calorie diet regimen in some kinds of obese diabetic patients. Because metabolic and cardiovascular diseases are multi-factorial phenomena, we need to consider the effect of other metabolic disorders such as dyslipidemia, hypercholesterolemia, and hypertension on the expression of adiponectin. Table 3 summarizes the effects of CR, weight loss and gastric bypass surgery on adiponectin.

CONCLUSIONS

There is no doubt that pharmacological agents and lifestyle modifications affect metabolic and cardiovascular disease. In regard to the expression of adiponectin and its receptors with these interventions, it remains unclear whether these interventions ameliorate metabolic and cardiovascular dysfunction through adiponectin and its receptors-mediated signaling pathways. Recent studies provide compelling evidence supporting the beneficial role of adiponectin in the metabolic and cardiovascular diseases. Although significant progress has made in understanding the molecular mechanisms that underlie the beneficial actions of adiponectin, it should be noted that large discrepancies exist among those studies based on experimental design including species, type of intervention, and the pathological condition. Further investigations in adiponectin signaling pathways will provide potential targets used for the therapeutic interventions in metabolic and cardiovascular disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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