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; Moshkani 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...
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 Waldhaeusl, 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 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, nor 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/d) | 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 hypercholes terolemic hypertension | Both | Simvastatin (20 mg) - Losartan (100 mg) (100 mg/daily) | 2 mo | Oral intake | Plasma | ELISA | ↑ 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 | Funahashi 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 | Calik 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 | Olonol 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 | Mostovik et al., 2013 |
| Rats (OLETF) | Male | Rosiglitazone (2 mg/kg/day) - Fenofibrate (100 mg/kg/daily) | 40 wk | In food | Serum | ELISA | ↑ APN = APN | Choi et al., 2006 |
| Rats (Wistar) | Male | Sucrose Rich Diet - SUCROSE Rich Diet (7 mol%)-FO Diet (2 mol) | 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 | Li et al., 2006 |
| Hamsters (Golden Syrian) | Male | Niacin (1,200 mg/kg) | 18 days | Oral gavage | AT | PCR | ↑ APN | Connelly et al., 2013 |
| Mice (db/db) | Male | Pioglitazone (10 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 | ELISA PCR | ↑ 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 | 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.
### Table 2. Effects of exercise on adiponectin and adiponectin receptors

| Subject or animal | Sex     | Type of exercise | Duration | Tissues | Methods  | Conclusion | References                  |
|-------------------|---------|------------------|----------|---------|----------|------------|-----------------------------|
| Healthy subjects  | Both    | Cycle ergometry  | 60 min   | 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 (After 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      | Jamurtas et al., 2006         |
| Obese subjects    | Both    | Aerobic exercise + hypocaloric (ExEypo) or eucaloric (ExEu) diet | 12 wk (5 days/wk) | Serum   | ELISA    | ↑ HMW/Total APN ↑ AdipoR1 and 2 | O’Leary et al., 2007 |
| Obese subjects    | Female  | Aerobic exercise (Bicycle ergometer) | 12 wk (5 days/wk) | Plasma  | ELISA    | = 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      | Maxell et al., 2005         |
| Caucasian subjects with NGT, IGT, and T2D | Both | Physical training | 4 wk (3 days/wk) | Serum   | ELISA    | ↑ APN      | Bluher et al., 2006         |
| Caucasian subjects with NGT, IGT, and T2D | Both | Physical training | 4 wk (3 days/wk) | Subcutaneous AT Skeletal muscle | PCR | ↑ AdipoR1 and 2 | Bluher et al., 2007 |
| Caucasian subjects with NGT, IGT, and T2D | Both | Physical training (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  | ELISA    | ↑ 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   | ELISA    | ↑ 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 Liver White adipose | PCR | ↑ 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.
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.

### 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               | 12 wk   | Serum   | ELISA   | ↑ APN       | Schulte et al., 2013 |
| Obese subjects   | Both| CR program       | 3 mo    | Plasma  | ELISA   | ↑ HMW APN   | Kobayashi et al., 2004 |
| Obese subjects   | Female| CR (≤ 600 kcal/day) | 5-6 mo  | Adipose | PCR     | ↑ 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 |
| Obese subjects   | Female| CR (low-calorie diet, less than 5% 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       | Plum et al., 2011 |
| Rats (F344/NSlc) | Male| CR               | 4 wk    | Serum   | ELISA   | = HMW APN   | Plum et al., 2011 |
| Rats (SD)        | Male| CR (40%)         | 6 mo    | Serum Skeletal muscle Adipose Skeletal muscle Adipose | PCR PCR PCR PCR | ↑ APN ↑ APN ↑ APN ↑ APN | Dai et al., 2013 |
| Rats (SD)        | Male| CR (40%)         | 26 wk   | Serum   | ELISA   | ↑ APN       | Corqueira et al., 2012 |
| Rats (SHRs)      | Male| CR               | 5 wk    | Plasma  | ELISA   | ↑ APN       | Corqueira 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/6)   | Male| CR               | 4 wk    | Plasma  | ELISA   | ↑ 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.
surgery, 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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