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Nutraceutical characteristics of the brown seaweed carotenoid fucoxanthin

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ABSTRACT

Fucoxanthin (Fx), a major carotenoid found in brown seaweed, is known to show a unique and wide variety of biological activities. Upon absorption, Fx is metabolized to fucoxanthinol and amarouciaxanthin, and these metabolites mainly accumulate in visceral white adipose tissue (WAT). As seen in other carotenoids, Fx can quench singlet oxygen and scavenge a wide range of free radicals. The antioxidant activity is related to the neuroprotective, photoprotective, and hepatoprotective effects of Fx. Fx is also reported to show anti-cancer activity through the regulation of several biomolecules and signaling pathways that are involved in either cell cycle arrest, apoptosis, or metastasis suppression. Among the biological activities of Fx, anti-obesity is the most well-studied and most promising effect. This effect is primarily based on the upregulation of thermogenesis by uncoupling protein 1 expression and the increase in the metabolic rate induced by mitochondrial activation. In addition, Fx shows anti-diabetic effects by improving insulin resistance and promoting glucose utilization in skeletal muscle.

Keywords: Brown seaweeds, Fucoxanthin, Anti-obesity, Anti-diabetes, Anti-cancer

1. Introduction

Seaweeds (marine macroalgae) are photosynthesizing plants that form the basic biomass in the intertidal zone. They are a varied group, with sizes ranging from a few

centimeters to 100 m in length. According to their color, they are divided into three main classes: green (chlorophytes), red (rhodophytes), and brown (phaeophytes). Brown seaweeds are the most consumed species, followed by red and green seaweeds [1]. As seaweeds lack many of the distinct organs (roots, stems, leaves) found in terrestrial plants, whole parts can be used as a source of food, cosmetics, and other products. They have high nutritional value, in both fresh and dried forms, and act as ingredients in a wide variety of prepared foods.

The unique and phenomenal biodiversity of the marine environment provides a large pool of novel and bioactive nutrients for marine organisms. Seaweed is one of the potential sources of these marine bioactive compounds. Seaweed has been consumed in East Asian countries for centuries, and lately, knowledge of the health benefits of dietary seaweed has gained attention in Western cultures [2,3]. According to the Seafood Source report, new products containing seaweed in the European market have increased yearly [2]. Seaweed is rich in non-starch polysaccharides, mainly dietary fibers, and essential minerals such as potassium and calcium [4,5]. The quality of seaweed protein is comparable to other vegetables, mainly due to its high content of essential amino acids. The lipid content of seaweed is generally low, but seaweeds contain high levels of functional omega-3 eicosapentaenoic acid and omega-6 arachidonic acid [5]. Additionally, the value of edible seaweed in human nutrition is strongly recognized for its richness in several phycochemicals. Consequently, seaweed is currently considered a “superfood”, which is a market term recognizing health benefits including superior nutritional profile and richness in bioactive phytochemicals [6].

Primary metabolites of seaweed, such as polysaccharides, proteins, and lipids, are directly involved in their physiological functions under normal growth conditions, while the exposure to different stress conditions, (e.g., ultraviolet radiation, changes in temperature and salinity, or environmental pollutants) stimulates them to produce a wide range of secondary metabolites [6,7]. Among these secondary metabolites, much interest has been paid to seaweed antioxidants [2,6,8-13]. Compared to its terrestrial counterparts, seaweed is potentially a good source of antioxidants and has an advantage over many other organisms in that it can appropriately produce a large amount of desirable and specific bioactive compounds.

Alcoholic extracts from seaweed have been reported to show antioxidant activity due to the presence of polyphenols in the extracts. Red and green seaweeds contain bromophenols, phenolic acids, and flavonoids as the major polyphenols, while phlorotannins are only dominant in brown seaweed [8,14]. Phlorotannins are a group of

complex polymers of phloroglucinol (1,3,5-trihydroxybenzene). Based on the type of structural linkage between the phloroglucinol sub-units, they can be systematically classified into eckols, fucols, fuhalols, ishofuhalols, phloroethols, or fucophloroethols [2]. Many studies have shown that phenolic extracts from seaweeds have several kinds of biological activities [2,6,7,9,15-17]. Although these effects may be due to their ability to modulate oxidative stress and inflammatory cascades, the detailed mechanism remains unclear, mainly due to their complex chemical structure and the difficulty of identifying metabolites and active compounds after absorption.

Carotenoids are also major seaweed antioxidants. They are generally localized in photosynthetic organisms and play an important role in photochemical events [18]. β-Carotene, α-carotene, zeaxanthin, lutein, violaxanthin, neoxanthin, and fucoxanthin (Fx) has been reported in several kinds of seaweed [19]. Among these carotenoids, Fx is a specific carotenoid only found in algae but not terrestrial plants. Fx is photosynthetic pigment mainly found in brown seaweed and Bacillariophyta (diatoms). These algae are widely distributed in cold and temperate ecosystems throughout the world; therefore, Fx is regarded as one of the most abundant carotenoids in nature [20]. In addition to the important role of Fx in the photosynthesis and photoprotection of algae, Fx also has health benefits [21].

This article focuses on the current scientific literature regarding the bioactive significance of Fx, including metabolic, anti-oxidant, anti-obese, anti-diabetic, and anti-cancer activities,.

2. Structure and safety

Fx has a distinctive structure with an allenic bond, a 5,6-monoepoxide, and nine conjugated double bonds (Fig. 1). The conjugated double bond system in the Fx molecule can quench singlet oxygen ($^1O_2$) and the electron-rich status of Fx makes it more suitable to react with free radicals [21]. Therefore, Fx can protect cells, tissues and other structures against oxidative damage; however, it would be difficult to explain all of its beneficial health effects only by its antioxidant activity [22]. Much attention has been paid to the interaction between Fx or its metabolite and biological key molecules such as receptors and co-activators, where the specific chemical structure of a carotenoid may be essential for binding. To better understand the physiological effect of Fx, more efforts are needed to clarify the ability of Fx or its metabolites in modulating the expression of specific genes and proteins involved in biological systems (Fig. 2).

Fx-rich brown seaweed has been used in Southeast Asian countries as a traditional food. In addition to its use as a food source, the safety of Fx has been demonstrated through animal experiments. A single dose study indicated no mortality and no abnormalities in male and female ICR mice fed 1000 and 2000 mg/kg purified Fx. In a repeated dose study, no adverse effect of purified Fx was observed in mice given 500 and 1000 mg/kg Fx for 30 days [23] and in rats given 200 mg/kg Fx as Fx-containing oil for 13 weeks [24]. Additional animal studies [25-27] and a human study [28] confirmed that Fx caused no toxicities. On the basis of remarkable biological properties and safety, Fx can be considered a nutraceutical ingredient and can be utilized in the food industry and other fields to design new and improved nutraceuticals.

3. Absorption and metabolism

An *In vitro* study showed the hydrolysis of Fx to fucoxanthinol (FxOH) during absorption by Caco-2 cells [29] and the transformation of FxOH into amarouciaxanthin A in human hepatoma HepG2 cells [30] (Fig. 2). An animal study also revealed that dietary Fx is rapidly hydrolyzed to FxOH in the gastrointestinal tract by digestive enzymes, such as lipase and cholesterol esterase within 2 h of administration [30,31]. FxOH was further converted into amarouciaxanthin A through dehydrogenation/isomerization in mice liver microsomes and in HepG2 cells [30,32]. Although FxOH and amarouciaxanthin A have been detected in plasma and all tissues of mice given Fx [30,32-34], most Fx metabolites preferentially accumulate as amarouciaxanthin A in the visceral WAT [33,35]. Yonekura et al. [36] have also reported the preferential accumulation of Fx metabolites in visceral WAT, while these researchers observed that lutein and its metabolites mostly accumulated in the liver. On the other hand, some researchers have demonstrated the absorption of Fx without conversion to any metabolites [33,37].

Several studies have discussed the bioavailability of Fx in cellular, animal, and human models. The absorption rate of Fx in Caco-2 cells was reported to be the lowest out of 11 carotenoids tested [38]; however, the study only analyzed intact Fx but not its metabolites. Based on animal studies showed the ratio of absorbed Fx to the dose calculated using metabolite analysis, FxOH and amarouciaxanthin A exhibited higher levels than astaxanthin [33]. Other animal studies showed that Fx is absorbed in a similar fashion to β-carotene or lutein [30,39,40]. Furthermore, those authors concluded that Fx is more efficiently absorbed than lutein esters. In contrast, Hashimoto et al. [41] demonstrated from a human pharmacokinetics study that the bioaccessibility of Fx

seems to be lower than that of other carotenoids such as β-carotene, lutein or astaxanthin, while they demonstrated that the bioavailability of Fx was higher in human subjects than in mice. To increase bioaccessibility and stability of Fx, many challenges have been done [2]. They include encapsulation of Fx into nanoemulsions, nanoparticles, and other spray-dried powders.

Fx supplementation in a mouse model of obesity effectively decreased excess fat accumulation in abdominal white adipose tissue (WAT). This activity has been reported with at least 60 mg Fx intake/kg mouse/day [35]. On the other hand, a human study demonstrated a significant reduction in the abdominal WAT of obese female volunteers with an intake of Fx less than 0.024 mg/kg/day (2.4 mg intake/day for volunteers with 100 kg average weight) [42]. This difference in the effectiveness between rodents and humans may be due to different absorption rates and/or different sensitivities to Fx. Overall, Fx may be effective even at low levels.

4. Biological activities

4.1. Antioxidant activity

As seen in other carotenoids, Fx can quench singlet oxygen through a physical interaction, where the excess energy of singlet oxygen is transferred to the conjugated polyene structure of Fx [43-45] (Fig. 1). Fx with added energy is excited to a triplet state upon losing energy as heat relaxes to a singlet state without structural changes. The singlet oxygen quenching activity of a carotenoid is generally influenced by the number of conjugated double bonds [45,46]. In addition, the activity is also affected by other factors such as the chain structure and functional groups of carotenoids, solvent viscosity, and substrate dispersion system [47-50]. Sachindra et al. [51] reported that Fx has 9 conjugated double bonds and has a lower quenching ability of singlet oxygen than β-carotene (11 conjugated double bonds), while Hirayama et al. [48] reported little difference in quenching ability between Fx and β-carotene. Further, more effective prevention of lipid hydroperoxide formation by Fx was found in singlet oxygen-mediated plasma lipid oxidation than by β-carotene and α-tocopherol [52].

Another role of Fx as an antioxidant is attributed to the scavenging of a wide range of free radicals (Fig. 1). Fx has a unique chemical structure including an allenic bond, epoxide group, and hydroxyl group. The electron-rich status of Fx makes it more suitable for reactions with the free radicals [21]. Several studies have reported an effective radical scavenging ability of Fx [53]. Although a detailed mechanism has not

yet been determined, Fx can quench different kinds of free radicals such as 1,1-diphenyl-2-picrylhydrazyl (DPPH) [51,54-57], 2,2′-azinobis-3-ethylbenzo thizoline-6-sulphonate (ABTS) [51,57], hydroxyl [51,57], superoxide [51,57], and peroxy [58] radicals.

On the basis of the potential antioxidant properties of Fx, researchers examined the preventive effect of Fx on oxidative damage in biological systems. Murakami et al. [59] screened 19 natural carotenoids for their structure-function relationship with respect to radical scavenging activity. They found that the presence of an allenic bond, as seen in Fx and halocynthiaxanthin, increases the ability to inhibit the formation of superoxide in human promyelocytic HL-60 cells and of nitric oxide in mouse macrophage RAW 264.7 cells. Fx significantly reduced ROS production and the viability of oxidatively damaged monkey kidney fibroblast cells [60], human HaCaT keratinocytes [61], human hematoma HepG2 cells [62], and normal human hepatic L02 cells [63]. The antioxidant activity of Fx has also been reported *in vivo*. When oxidative stress was induced by retinol deficiency in rats, Fx significantly reduced lipid hydroperoxide levels of plasma, liver, and liver microsomes [64]. In another animal experiment [65], Fx supplementation significantly increased the total antioxidant capacity in plasma. The antioxidant activity of Fx is not only based on its singlet oxygen and free radical scavenging activities but also strongly related to its upregulation of antioxidant enzymes such as catalase [64] and gluthathione peroxidase [65]. In the upregulation pathway, several studies have demonstrated the involvement of the activation of Akt/nuclear factor-erythroid 2-related (Nrf2) by Fx [63,65,66].

4.2. Anti-obesity effect

Many reviews have been published on the protective effects of Fx against various diseases [7,21,53,67-76] (Fig. 2). Of all characteristics of Fx, anti-obesity is certainly the most well-studied and promising [21,67,68,70,72,76].

Anti-obesity properties of Fx were first discovered in rats and mice given brown seaweed lipids containing Fx [77]. This effect has been confirmed using various animal models [78-84]. In addition, a comparative study indicated that Fx attenuates excess fat accumulation in the abdominal WAT of the obese KK-A^y mice [79] and of C57BL/6J mice fed a high-fat diet [83], while no effect was found in the C57BL/6J mice fed a normal-fat diet [79]. These results suggest the suppressive effect of Fx on WAT weight gain is specific for adiposity in the development of obesity in mice. This specificity will be important for the safe application of Fx in human therapies for obesity. In a human

clinical trial, 2.4 mg Fx daily for volunteers (average weight 100 kg) resulted in a significant decrease in body fat, body weight, liver fat content, and serum triglyceride levels, which was accompanied by improvement in liver function tests [42]. The clinical trial also demonstrated an increase in the resting energy expenditure after >2.4 mg Fx intake. Hitoe and Shimoda [28] also examined the effect of Fx on mildly obese Japanese volunteers and reported a significant reduction of relative body weight, body mass index, and visceral fat area after 3 mg daily Fx intake for 4 weeks. Relative values of total fat mass, subcutaneous fat area, waist circumference, and right thigh circumference were also significantly lower after 1 mg Fx intake compared to the placebo group. Another study reported the induction of BAT expression by Fx intake in obese human subjects assessed by 18F-fluorodeoxyglucose-positron emission tomography [85].

Obesity is defined as a condition of excess body fat induced by increased energy intake and/or reduced energy expenditure. Obesity is associated with a large number of metabolic disorders that induce cardiovascular and various other non-communicable diseases. Lifestyle interventions, such as a change in dietary habits and increased physical activity, are fundamentally important to obesity therapy [86]. In addition to these essential interventions, much attention has been paid to nutritional and dietary factors, especially metabolically active food compounds. Major molecular mechanisms for controlling obesity with nutrition include reducing food intake through the control of signals from the gut and adipose tissue; inhibiting nutrient absorption; increasing thermogenesis to dissipate food energy as heat; and modulating fat synthesis/lipolysis or adipose differentiation/apoptosis [87,88]. Many functional food components have been shown to alter energy metabolism by influencing fat absorption, substrate utilization rate, and thermogenesis.

Upregulation of sympathetically mediated thermogenesis is the most targeted component when developing functional foods for obesity therapy. Uncoupling protein 1 (UCP1) expression is a major factor in this thermogenic process. UCP1 can be induced in brown adipose tissue (BAT) [89-91] and in beige adipocytes of WAT [92-94]. Although several mechanisms have been proposed for the anti-obesity effects of Fx, adaptive thermogenesis via UCP1 induction in adipose tissue is the major target of Fx [21,22,53,68,72,73,95] (Fig. 3). Activated UCP1, short circuits the electrochemical gradient normally used to drive adenosine triphosphate (ATP) synthesis. This can occur with the re-entry of protons into the mitochondrial matrix, bypassing ATP synthase. The uncoupling of oxidative phosphorylation releases excess energy intake as heat. Feeding Fx to mice increased BAT weight and induced UCP1 mRNA and protein expressions in abdominal WAT [77,81,82], suggesting that the anti-obesity effect of Fx is derived from

an increase in the adaptive thermogenesis through UCP1 expression. In addition, Fx supplementation in animal models increased the mRNA and protein expression of several biomolecules, such as β3-adorenarine receptor (β3Ad) and peroxisome proliferator-activated receptor gamma co-activator 1 (PGC-1), in WAT [83,96]. The upregulation of β3Ad and PGC-1 are known to positively regulate UCP-1 expression [21]. Furthermore, PGC-1 upregulation can also induce mitochondrial biogenesis. Therefore, the anti-obesity effect of Fx would also be related to the increase in metabolic rate induced by mitochondrial activation [97] (Fig. 3).

Several studies have also shown that Fx ameliorates obesity through its effects on lipid metabolism. Woo et al. [98] reported an increase in the content of non-digested fecal lipids and a decrease in hepatic lipid and plasma triacylglycerol levels by Fx supplementation to C57BL/6N mice fed a high-fat diet. The effect of Fx could be explained by reduced activity of hepatic lipogenesis and enhanced activity of fatty acid β-oxidation [98,99]. In another study using obese mice fed a high fat diet [84], the mRNA expression and activity of lipogenic enzymes were significantly downregulated in a dose-dependent manner in epididymal adipose tissue, with simultaneous upregulation of fatty acid β-oxidation. In addition, Fx increased the activities of key enzymes in lipid metabolism, such as AMP-activated protein kinase and its downstream target acetyl-CoA carboxylase in epididymal adipose tissue of diet-induced obese mice [80]. Moreover, Fx and FxOH have been demonstrated to inhibit pancreatic lipase activity and suppress triacylglycerol absorption after oral infusion with oil [31]. Improvement of hepatic lipid metabolism by Fx intake would be related to risk reduction in non-alcoholic fatty liver disease (NAFLD) [100]. Potential protective functions of Fx against the development of NAFLD have also been recognized in a human study [42]. Consumption of an Fx supplement containing 2.4 mg of pure Fx for 16 weeks decreased liver fat content and serum concentrations of TAG and C-reactive protein in obese premenopausal women with NAFLD.

The regulatory effect of Fx and Fx metabolites on adipocyte differentiation may be involved in its anti-obesity effects [21,73]. These compounds suppressed murine pre-adipocyte differentiation to mature adipocytes by inhibiting intracellular lipid accumulation and decreasing glycerol-3-phosphate dehydrogenase activity [101,102]. When the suppressive effect of Fx and Fx metabolites on the differentiation of 3T3-L1 preadipocytes to adipocytes was compared [101,102], amarouciaxanthin A showed the strongest effect, followed by FxOH and Fx. Fx and FxOH downregulated adipogenic genes, such as peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer binding protein α (C/EBPRα), in a dose-dependent manner. On the

other hand, Kang et al. [103] has demonstrated that the effect of Fx on adipocytes depends on its differentiation stage, early (days 0-2), intermediate (days 2-4), and late stage (days 4-7). Fx paradoxically promoted adipocyte differentiation during the first two days by increasing the expression of PPARγ, C/EBPRα, sterol regulatory element-binding protein 1c, and adipocyte fatty acid-binding protein, while it inhibited differentiation at later stages by reducing these protein expression levels.

Okada et al. [104] compared the suppressive effect of 13 naturally occurring carotenoids on the differentiation of 3T3-L1 adipose cells. Among these carotenoids, neoxanthin did show suppressive effects on lipid accumulation, glycerol-3-phosphate dehydrogenase (GPDH) activity and adipocyte protein 2 expression in the 3T3-L1 differentiation. However, treatment with (rac)-α-carotene, carotenoids with keto group (citranaxanthin, rhodoxanthin, canthaxanthin) and an epoxy group (β-carotene 5,6-epoxide) did not result in apparent changes in the level of GPDH activity. The same was true for hydroxyl carotenoid (β-cryptxanthin, lutein), epoxy-hydroxy carotenoids (violaxanthin, antheraxanthin, lutein epoxide), and keto-hydroxy cerotenoids (capsorubin). Interestingly, neoxanthin contain allenic bond, a 5,6-monoepoxide, and three hydroxyl groups and this structure is very similar in structure to FxOH and amarousiaxanthin A, major metabolites of Fx. These findings provide further evidence for the theory that suppressive effect on adipocyte differentiation in carotenoids are related to structural properties, where allenic bond is essential for the expression of the activity.

4.3. Anti-diabetic effect

Obesity has been recognized as a driver of type 2 diabetes [105]. Indeed, the majority of patients with type 2 diabetes are obese [106], and the increased incidence of type 2 diabetes has paralleled that of obesity. Excess fat accumulation in abdominal WAT in obese individuals increases the secretion of biologically active mediators, termed adipokines/chemokines, from adipocytes, as part of the endocrine system [21]. Development of obesity leads to an increase in pro-inflammatory adipokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1. These pro-inflammatory adipokines induce macrophage infiltration into the abdominal WAT, leading to chronic low-grade inflammation. Furthermore, saturated fatty acid and TNF-α derived from adipocytes and macrophages, respectively, initiate a paracrine loop that leads to inflammation in the adipose tissue and upregulation of pro-inflammatory adipokine secretions. These adipokines are reported to increase

insulin sensitivity [107]. On the other hand, Fx supplementation significantly inhibited macrophage infiltration and downregulated pro-inflammatory adipokine expression and secretion in the abdominal WAT of obese/diabetes KK-A^y mice, resulting in the improvement of insulin resistance and subsequent blood glucose levels [79,82]. Normalization of blood glucose levels by Fx intake has also been observed in C57BL/6J mice fed a high fat diet [83,98,99], while Fx did not affect the blood glucose levels in C57BL/6J mice fed a normal diet [79], suggesting the specificity of the lowering effect of Fx on diabetes.

Another possible mechanism for the anti-diabetic effect of Fx is the regulation of glucose transporter 4 (GLUT4) [83,96]. GLUT4 protein is the predominant isoform of the glucose transporters expressed abundantly in skeletal muscle and adipose tissue. With insulin and other stimuli, GLUT4 expression is upregulated, quickly moves to the plasma membrane from an intracellular location, and promotes glucose uptake [108]. However, in type 2 diabetes mellitus, insulin signaling is impaired and GLUT4 expression and its translocation is attenuated [109]. When mice were fed high fat (HF) or normal fat (NF) diets, the HF group experienced hyperglycemia, hyperinsulinemia and hyperleptinemia with a significant decrease in GLUT4 mRNA levels in skeletal muscle compared to the NF group [83]. These disorders were completely normalized by the addition of Fx to the HF diet, and GLUT4 mRNA levels in the HF group with Fx were restored to levels observed in the NF group. These anti-diabetic effects of Fx were recapitulated in obese/diabetes KK-A^y mice [96]. A significant increase in GLUT4 levels was found in the extensor digitorum longus muscle of the obese/diabetes mouse model together with an upregulation of PGC-1α expression [96]. PGC-1α is an important co-activator that has been implicated in the regulation of mitochondrial biogenesis and the activation of GLUT4 [110,111]. In addition, Fx supplementation significantly increased GLUT4 translocation to plasma membranes from the cytosol in the soleus muscle of KK-Ay mice.

4.4. Anticancer activity

Compared with other carotinoids, Fx is known to exhibit stronger anti-proliferative effects on several cancer cell types [69,112]. Fx strongly decreased the viability of many cancer cell types such as human neuroblastoma GOTT [113], leukemia (HD-60) [114], epithelial colorectal adenocarcinoma (Caco-2, DLD-1 and HT-29) [115], human prostate cancer (PC-3) [116], mouse melanoma (B16) and human colorectal carcinoma (HCT116) [117], while it did not affect the normal cell viability [117]. Kotake-Nara et

al. [118] compared the effect of 15 kinds of carotenoids (phytoene, phytofluene, ξ-carotene, lycopene, α-carotene, β-carotene, β-cryptoxanthin, canthaxanthin, astaxanthin, capsanthin, lutein, zeaxanthin, vioaxanthin, neoxanthin, and fucoxanthin) present in foodstuffs on the growth of human prostate cancer cell lines (PC-3, DU 145 and LNCap). Among the carotenoids evaluated, allenic carotenoids, neoxanthin and Fx, showed the higher activity in the growth reduction of these prostate cancer cells as compared with other kinds of carotenoids without allenic bond, suggesting the importance of allenic bond in the anti-proliferative ability of carotenoids.

Fx intake also suppressed the number and growth of tumors in animal models [119-122]. In addition, brown seaweed extract (containing Fx showed chemopreventive activity against the formation of aberrant crypt foci, a preneoplastic marker for colon cancer, in rats [123,124]. To investigate the underlying mechanisms of the anti-cancer potential of Fx, many studies have focused on several biomolecules and signaling pathways involved in either cell cycle arrest, apoptosis, or metastasis suppression [37,67,69,71,112]. These studies suggest that Fx could arrest the cell cycle of tumor cells in the G0/G1 and/or G2/M phase by altering the expression of various genes including upregulating GADD45, p21 and p27 and downregulating cyclin D1, cyclin D2, CDK4, and survivin [37,67,69,71,75,112,125]. The apoptotic effect of Fx is well-studied because apoptosis of cancer cells is a promising method to control and treat cancer. Fx induces apoptosis by targeting different molecular pathways including Bcl-2, caspase, mitogen-activated protein kinase, nuclear factor kappa B families, and others [69,71,75].

Recently, efforts have focused on the chemopreventive effect of Fx in colorectal cancer. Takahashi et al. [126] found that FxOH showed higher anti-proliferative activity than Fx on different kinds of colorectal cancer cell lines including DLD-1, HCT116, SW620, Caco-2, Colo205, and WiDr. The anti-proliferative capacity of FxOH was also effective in colorectal cancer stem cells ($CD44^{high}$ and $EpCAM^{high}$ cells) [127]. These cells initiate colorectal carcinogenesis and play a central role in tumor development, exhibiting several biological properties including self-renewal, multipotential, drug-resistance, sphere formation, and tumor formation in xenograft models. FxOH significantly inhibited the growth of the colorectal cancer stem cells [127]. Fx also suppressed sphere-forming activity, migration and invasion of colorectal cancer stem cells in a dose-dependent manner [128] and downregulated several biomolecules related to cell proliferation, cell cycle, metastasis, and extracellular adhesion [127]. In addition, Fx induced anchorage-dependent apoptosis in human colorectal cancer (CRC) cells through the suppression of integrin signals [129,130]. In animal models, Fx

396 administration significantly suppressed tumor development in a xenograft model of
397 colorectal cancer [127,131], decreased the number of colorectal polyps, and decreased
398 colonic lesions compared to untreated control mice [132]. In addition, Fx administration
399 resulted in significantly lower numbers of colorectal cancer stem cell-like cells,
400 cancer-associated fibroblast-like, tumor-associated macrophage-like and dendritic
401 cell-like cells in colonic mucosa compared to untreated control mice [132].
402
403 *4.5. Other activities*
404
405 Given that metabolic syndrome and obesity are regarded as major risk factors for the
406 induction of cardiovascular disease (CVD), much attention has been paid to the
407 anti-obesity and anti-diabetic effects Fx. In addition, Fx is known to show *in vivo*
408 anti-oxidant, anti-inflammatory, and anti-hypertensive activities. These abilities are also
409 important in the context of CVD. The antioxidant activity of Fx has been well-described,
410 and several studies have reported anti-inflammatory [7] and anti-hypertensive [53,133]
411 activities of Fx. Effective downregulation of lipopolysaccharide-induced inflammatory
412 signaling pathways has been found in cellular models supplemented with Fx [134-136].
413 In these models, Fx significantly suppressed the expression and secretion of
414 inflammatory mediators such as nitric oxide, prostaglandin E_2, TNF-α, IL-6, and IL-1β
415 and inflammatory cytokines such as cyclooxygenase (COX) and inducible nitric oxide
416 synthase (iNOS) [137]. The levels of inflammatory markers such as IL-1β, TNF-α,
417 iNOS, and COX-2 were downregulated in an obese mouse model [138]. The protective
418 effect of fucoxanthin was further described in UV-induced inflammation in cellular
419 [139] and animal [140] models. Fx has also been reported exhibit anti-hypertensive
420 properties. Supplementation of brown seaweed containing Fx delayed the incidence of
421 stroke symptoms and increased the life span of stroke-prone spontaneously hypertensive
422 rats [141], although there was no significant difference in the blood pressure with Fx
423 intake. Fx isolated from brown seaweed may also have a preventive effect on ischemic
424 cultured neuronal cell death. An interesting, extra metabolic effect of Fx is the
425 promotion of the synthesis of docosahexaenoic acid (DHA) in the liver, resulting in
426 improvements in the lipid profile [34,142]. DHA is known to positively influence
427 human nutrition and health including cardioprotection. DHA could inhibit the
428 development of inflammation in endothelial cells, alter the function and regulation of
429 vascular biomarkers, and reduce cardiovascular risk [143]. It can also improve
430 hypertriglyceridemia, which is known to increase cardiovascular risk [144]. Therefore,
431 the protective effect of Fx on CVD maybe explained by an increase in DHA levels.

Fucoxanthin protected neuronal cells against oxidative damage induced by H_2O_2 [145,146] and oligomers of β-amyloid (Aβ) [147,148]. This effect involved the activation of PI3-K/Akt cascade and inhibition of ERK pathway by Fx [146,148]. Aβ oligomers are known as major neurotoxins in Alzheimer's disease (AD). Fx potently reduced the formation of Aβ oligomers *in vitro* and *in vivo* [149]. In the brains of AD patients, neuronal degeneration is accompanied by markers of microglial activation and inflammation, as well as oxidant damage. Fx can ameliorate oxidative stress and inflammation in Aβ42-induced BV2 microglia cells [150]. In addition, Fx plays a protective role in animal models of traumatic brain injury [151] and middle cerebral artery occlusion [152]. Although the underlying mechanism of the neuroprotective effect of Fx has not been fully elucidated, molecular docking studies suggest the importance of interactions between Fx and key proteins related to brain function [153]. Paudel et al. [154] have shown that Fx could serve as a potent dopamine D3/D4 agonist that might be useful in the management of neurodegenerative diseases, especially Parkinson's disease. On the other hand, β-site amyloid precursor protein cleaving enzyme 1 (BACE1) levels are known to be elevated in sporadic AD brains at disease onset. The BACE1 levels are upregulated under stress conditions such as cerebral ischemia, hypoxia, and oxidative stress. Fx inhibited the BACE1 activity through the interaction between two hydroxyl groups on the Fx molecule and two additional BACE1 residues (Gly11 and Ala127) [155].

5. Fx source and its extraction

Although Fx can be synthesized chemically, extraction from brown seaweed is a more accessible, safe, and economic method [75]. The Fx content in brown seaweed varies greatly by species, geographical location, season, temperature, salinity, and light intensity, as well as interactions among these factors [5]. Comparative studies on 15 brown seaweed samples collected near the northern coast of Japan have revealed that higher levels of Fx were found in *Sargassum horneri* (Turner) (370 mg/100 g dry weight) and *Cystoseira hakodatensis* (Yendo) (240 mg/100 g dry weight) [156]. The same research group also examined seasonal changes in the lipid components of the two brown seaweeds, *S. horneri* and *C. hakodatensis* [157]. They collected young thalli of both brown seaweeds cultivated in the northern coast of Japan. The Fx content of both brown seaweeds increased from October/November, reached a maximum in January, and decreased thereafter. In January, the Fx content of *S. horneri* and *C. hakodatensis* was 449 mg and 363 mg/100 g dry weight, respectively. Furthermore, by controlling the

468 cultivation conditions, such as temperature, light, and depth, a high content of Fx (1080
469 mg/100 g dry weight) was found in *S. horneri* cultivated in cold water [158].
470 Fx is generally extracted from brown seaweed with organic solvents [159-166].
471 However, recovery remains low due to the presence of various physical and chemical
472 barriers in the complex matrix. In addition, conventional extraction methods are
473 time-consuming and require a large amount of organic solvent. To overcome the
474 disadvantages of conventional solvent extractions, several studies have reported
475 advanced techniques, such as pressurized liquid extraction [167], enzyme-assisted
476 extraction [168], and extraction with supercritical CO_2 [169-173]. Much interest has
477 been generated in the development of new, eco-friendly alternatives to petrochemical
478 organic solvents. These ideal alternative "green" solvents, should be nontoxic,
479 bio-based, and environmentally friendly. Supercritical CO_2 is regarded as a green
480 solvent. However, this method requires expensive investment and a complex operating
481 system with high operating costs [174-176]. In addition, the solubility of Fx in
482 supercritical CO_2 is low, requiring the use of cosolvents [172].
483 Considering the increase in consumer concern regarding organic solvent
484 contamination in the final food product, the development of new eco-friendly solvents is
485 still required. The use of edible oils for the extraction of Fx from brown seaweed is
486 promising. Edible oils are regarded as green alternative solvents with no volatile organic
487 compounds, low toxicity for humans, and a limited impact on the environment. Due to
488 their oil solubility, carotenoids can be extracted with edible oils from natural resources.
489 Products from carotenoid extraction with edible oils can be directly used as food
490 materials without purification, and the oil protects carotenoids from degrading [177].
491 This advantage is not found using other green extraction methods. When the edible oil
492 used for carotenoid extraction shows any type of nutritional functionality, as seen in
493 omega-3 oils [178,179], medium-chain triacylglycerol (TAG) (MCT) [180-182], olive
494 oil [183,184], and others, the extracts are expected to show the combined biological
495 activities originating from phytochemicals such as carotenoids and from the functional
496 oils.
497 Although several studies have highlighted many advantages for extracting
498 carotenoids with edible oils from shrimp waste [185-188], crawfish waste [189-191],
499 microalgae, *Haematococcus pluvialis* [192,193], and fresh carrots [194], little is known
500 about their application to Fx extraction. Recently, Teramukai et al. [195] reported
501 effective extraction of Fx from brown seaweed, *Sargassum horneri*. When the
502 extraction rate was compared with 12 types of edible oils, more Fx could be extracted
503 with short-chain (tributylin, C4 and tricapronin, C6) TAG, medium-chain (tricaprylin,

C8) TAG (MCT), and fish oil compared with other edible oils; e.g., rice bran, rice germ, rapeseed, sesame, corn, soybean, and linseed [195]. MCT reportedly increases the anti-obesity effect of Fx [81]. WAT weight gain was markedly lower in diabetic/obese KK-A^y mice fed a mixture of Fx (0.1%) and MCT (0.9%) than in mice fed Fx (0.1%) alone. In addition, the expression of UCP1 was also markedly increased by MCT co-supplementation with Fx. Furthermore, an increase in anti-obesity and anti-diabetic effects of Fx has been reported with the combination of fish oil rich in EPA and DHA [82]. These results suggest that Fx extracts from brown seaweed with MCT and fish oil may show higher biological activities than those with organic solvent.

6. Conclusion

Since the discovery of the anti-obesity effect of Fx with UCP1 induction in abdominal WAT, many studies have been conducted on the nutritional impact of Fx. Increasing data clearly shows that Fx is effective at reducing the risk of a surprisingly wide variety of dysfunctions and diseases, including metabolic syndrome, obesity, heart disease, diabetes, cancer, hypertension, and reactive oxygen species- and inflammation-associated disorders. To explain the underlying mechanism, studies have demonstrated the modulation effect of Fx or its metabolites on signaling pathways related to these dysfunctions and diseases. The biological activities of Fx may be due to its unique chemical structure and its interaction with important biomolecules such as receptor proteins. Thus, more research is required to clarify the interactions by analyzing binding sites of the Fx molecule, the affinity for specific biomolecules, the molecular docking, etc.

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Figure legends

1224 Fig. 1. Antioxidant activity of Fx.

1225 Fig. 2. Major biological impact of Fx.

1226 Fig. 3. Major possible mechanism for the anti-obesity effect of Fx.

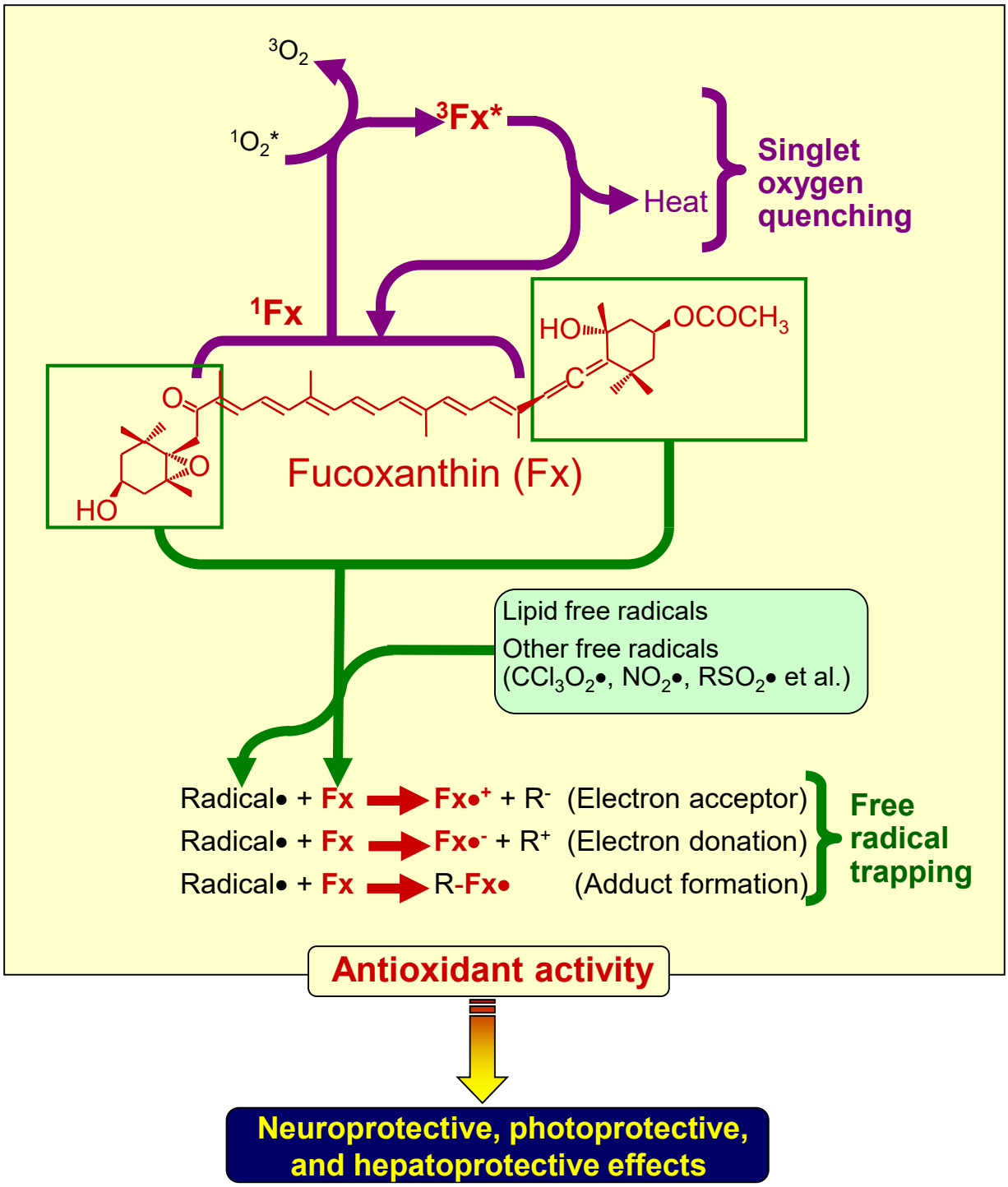
$^3O_2$
$^1O_2$*
^{3}Fx*
Heat
Singlet oxygen quenching
^{1}Fx
HO
OCOCH$_3$
O
O
HO
Fucoxanthin (Fx)
Lipid free radicals
Other free radicals
(CCl_3O_2•, NO_2•, RSO_2• et al.)
Radical• + Fx → Fx•$^+$ + R$^-$ (Electron acceptor)
Radical• + Fx → Fx•$^-$ + R$^+$ (Electron donation)
Radical• + Fx → R-Fx• (Adduct formation)
Free radical trapping
Antioxidant activity
Neuroprotective, photoprotective, and hepatoprotective effects

Fig. 1

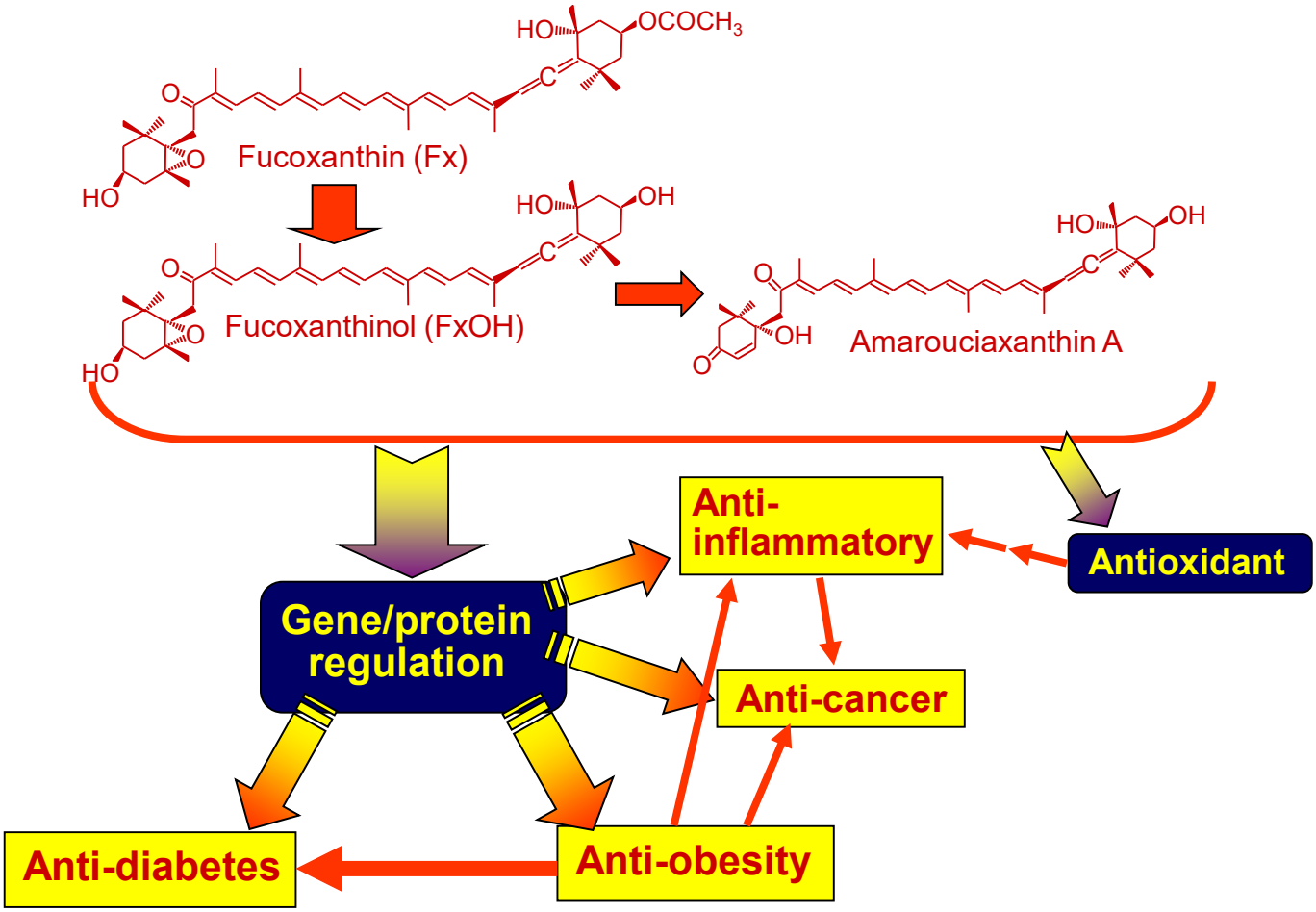
HO
OCOCH3
O
C
O
HO
Fucoxanthin (Fx)
HO
OH
O
C
O
HO
Fucoxanthinol (FxOH)
HO
OH
O
C
OH
O
Amarouciaxanthin A
Anti-
inflammatory
Antioxidant
Gene/protein
regulation
Anti-cancer
Anti-diabetes
Anti-obesity

Fig. 2

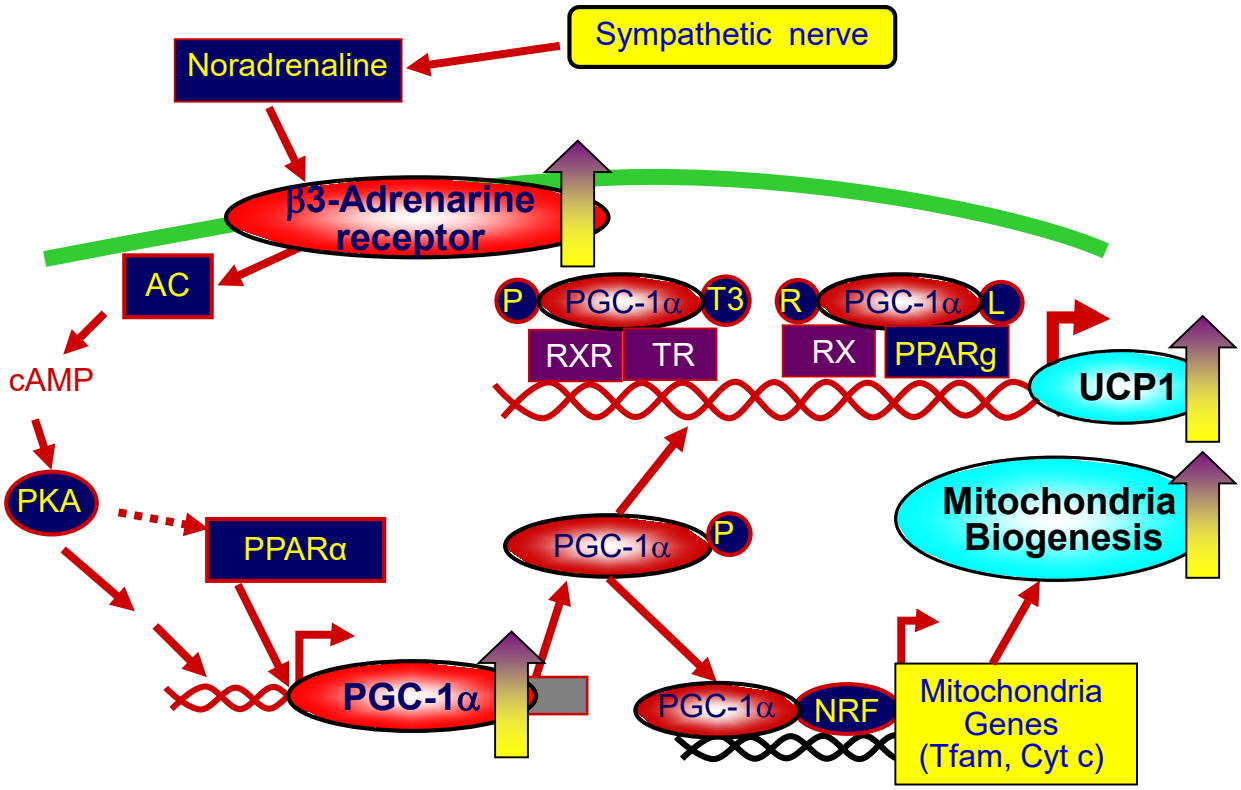
Sympathetic nerve
Noradrenaline
β3-Adrenarine receptor
AC
cAMP
PKA
PPARα
P
PGC-1α
T3
RXR
TR
R
PGC-1α
L
RX
PPARg
UCP1
PGC-1α
P
PGC-1α
PGC-1α
NRF
Mitochondria Biogenesis
Mitochondria Genes (Tfam, Cyt c)

Fig. 3