Journal of Sport and Health Research 2013, 5(3):237-250

Laupheimer, M. W.; Perry, M.; Malliaris, P.; Berdejo-del-Fresno, D.; Maffulli, N.; Hemmings, S. (2013). Resveratrol: A review of basic science and potencial indications in sports and exercise medicine. *Journal of Sport and Health Research.* 5(3):237-250.

Review

RESVERATROL: A REVIEW OF BASIC SCIENCE AND POTENTIAL INDICATIONS IN SPORTS AND EXERCISE MEDICINE

RESVERATROL: UNA REVISIÓN BÁSICA DE LA CIENCIA Y POSIBLES INDICACIONES EN MEDICINA DEPORTIVA Y DEL EJERCICIO

Laupheimer, M. W.[1, 2, 3]; Perry, M.[1]; Malliaris, P.[1]; Berdejo-del-Fresno, D.[3]; Maffulli, N.[1]; Hemmings, S.[1]

[1]*Queen Mary, University of London (United Kingdom)*

[2] *Sports & MSK Physician BUPA (United Kingdom)*

[3] *The English Football Association (United Kingdom)*

Correspondence to:
Markus W. Laupheimer
Sports & MSK Physician
7 The Elms
Thicket Road, Houghton
PE28 2FQ England
Email: markus@mskclinic.co.uk

Edited by: D.A.A. Scientific Section Martos (Spain)

editor@journalshr.com

Received: 26-03-2013
Accepted: 30-06-2013

Journal of Sport and Health Research 2013, 5(3):237-250

RESUMEN

Objetivos: Revisar la literatura para identificar las indicaciones del Resveratrol en medicina del deporte y sugerir futuras líneas de investigación.
Material y métodos: La literatura fue identificada, seleccionada y evaluada mediante una revisión sistemática. Publicaciones relevantes para identificar las indicaciones del Resveratrol fueron identificadas mediante una búsqueda en las siguientes bases de datos: PubMed, Cochrane Library, Google Scholar and Ovid. Resultados: Originalmente 962 artículos fueron identificados, de los cuales cinco fueron apropiados para la inclusión en esta revisión. 4 de ellos eran estudios experimentales animales con análisis in-vivo y ex-vivo, y uno fue un estudio doble-ciego, controlado con placebo en sujetos humanos. 3 de los cuatro estudios en animales mostraron una mejora de la resistencia de los ratones tratados con Resveratrol. Todos los estudios animales mostraron cambios básicos que apoyan la hipótesis de una posible mejora del rendimiento debido a cambios celulares y posibles mejoras adicionales de los efectos del ejercicio combinado con un tratamiento de Resveratrol.
Conclusiones: Resveratrol como suplemento alimenticio en medicina del deporte no ha recibido mucha atención, a pesar de las fuertes evidencias básicas que indican que esta sustancia podría tener múltiples indicaciones relacionadas con el alto rendimiento deportivo, así como la mejora de los beneficios del ejercicio para la población en general.

Palabras clave: Rendimiento, Beneficios para la salud, ser Humano, eliminación de grasa.

ABSTRACT

Objectives: To systematically review the literature to identify possible indications for Resveratrol in sports and exercise medicine and suggest future avenues of research.
Methods: Literature was identified, selected and appraised with the methods of a systemic review. Potentially relevant publications to answer the research question were identified by searching the following databases: PubMed, Cochrane Library, Google Scholar and Ovid.
Results: Originally 962 articles were identified, of which five were found to be appropriate for inclusion in the review. 4 of them were experimental animal studies with in-vivo and ex-vivo analysis and one was a double-blind, placebo controlled cross-over study with human subjects. 3of the four animal studies showed an endurance enhancement of the mice treated with Resveratrol. All of the animal studies showed basic changes to support the hypothesis of a possible performance enhancement due to cellular changes and possible additional improvement of effects of exercise combined with Resveratrol treatment.
Conclusion: Resveratrol as a food supplement in sports and exercise medicine has not received much attention, despite strong basic scientific evidence that this substance could have multiple indications related to high performance sports as well as enhancement of the health benefits of exercise for the general population.

Keywords: Performance, health benefits, humans, fat burning

Journal of Sport and Health Research 2013, 5(3):237-250

INTRODUCTION

Resveratrol is a natural polyphenolic flavonoid antioxidant, which may provide numerous health benefits, including the prevention of a wide variety of illnesses, including cancer (Baur & Sinclair, 2006; Markus & Morris, 2008), cardiovascular disease and ischaemic injuries, as well as enhancing stressresistance (Baur & Sinclair, 2006; Markus & Morris, 2008). It is freely available as a food supplement and is found in the seeds and skins of grapes, red wine, mulberries, peanuts and rhubarb (Baur & Sinclair, 2006; Markus & Morris, 2008; Naylor, 2009). Research suggests a diversity of health benefits by activating intracellular pathways which are the same as those activated by calorie restriction, an intervention long known to enhance health (Baur & Sinclair, 2006; Markus & Morris, 2008; Naylor, 2009).

In recent years, interest in Resveratrol has been increased by the quest to find an explanation for the ”French Paradox”, the observation that the French population has a much lower incidence of cardiovascular disease despite a high fat diet (Naylor, 2009).

As well as a role for Resveratrol in the prevention of various age and obesity related diseases, several animal studies have shown the ability to inhibit excessive aggregation of platelets, besides potent antioxidant and vasodilator action (Baur & Sinclair, 2006; Markus & Morris, 2008). Additional findings showed potential anti-inflammatory and immune-modulating actions via inhibition of cyclo-oxygenase activity (Baur & Sinclair, 2006; Markus & Morris, 2008; Naylor, 2009; Das& Das, 2007; Martin et al., 2006). The most striking effect and the one which has drawn the most attention is that Resveratrol produces changes associated with a longer lifespan (Baur & Sinclair, 2006; Markus & Morris, 2008; Baur et al 2006).

The aim of this review is to determine what research has been conducted with Resveratrol relating to sports and exercised medicine. So far no review about Resveratrol has focused on possible indications in Sports & Exercise Medicine (SEM), although several seem likely. This review was also undertaken to identify areas in which further research is needed.

METHODS

Searching

A search of the following electronic databases was conducted to identify scientific articles for inclusion: PubMed, Cochrane Library, Google Scholar and Ovid.

The search was restricted to publications available in English. The databases were searched up to August 2012. The reference list of reviews or articles was also searched for relevant articles. Inclusion criteria and search terms used were “Resveratrol” as the main search with the criteria of the SEM health and performance continuum. Examples of the search strategy used in PubMed and other databases are outlined in table 1.

TABLE 1. Example of search strategy in Medline and other database.

SEARCH STRATEGY
1. Revesratrol and Performance or Performance enhancement
2. Revesratrol and Sports Nutrition
3. Revesratrol and Exercise or Exercise physiology
4. Revesratrol and Doping
5. Revesratrol and Psychology
6. Revesratrol and Health and Health promotion
7. Revesratrol and Prevention and Preventative medicine
8. Revesratrol and Chronic medical conditions
9. Revesratrol and Rehabilitation
10. Revesratrol and Sport
11. Resveratrol and Wellness

Journal of Sport and Health Research 2013, 5(3):237-250

Study Inclusion

Potential articles were identified by evaluating the title and abstract for relevance to sports and exercise medicine. Full copies of potentially relevant studies were obtained for detailed examination. The reviewer excluded studies not relevant after an initial screening of the full text. Due to the novelty of the review there were only a very limited number of articles which fitted the inclusion criteria.

All of the studies reviewed have been basic research articles based on animal and in vitro research. The quality of the research was not assessed as an exclusion criterion due to the limited number of articles, but all the relevant studies were published in high quality high impact journals. To assess the relevance of sometimes highly complex research, further reading about performance and endurance was undertaken to identify further articles which could be included. As a result of the considerable variation in methodology of the studies and their complexity, a descriptive account of the studies was undertaken to characterise the research and identify strengths and weaknesses in this literature.

RESULTS

The search of all databases identified 962 unique articles. Based on the title and the abstract, 18 of those were identified for further evaluation. The areas where most results have been found were Resveratrol and performance, endurance, health and chronic medical problems. Resveratrol and the anti-inflammatory properties were a common result, but not within the inclusion criteria of this review although relevant for sports and exercise medicine. Out of the 18 articles, 5 studies (Baur et al, 2006; Lagouge et al, 2006; Mayers et al, 2009; Murase et al., 2009;Kennedy et al., 2010) were relevant to SEM and met the criteria of SEM health and performance continuum. Details of the included studies are presented in table 2. Out of the five studies, four (Baur et al, 2006; Lagouge et al, 2006; Mayers et al, 2009; Murase et al., 2009) were experimental animal studies with in-vivo and ex-vivo analysis and one (Kennedy et al., 2010) was a double-blind, placebo controlled cross over study with human subjects.

Performance Endurance

The four animal studies all assessed endurance of the mice used for the experiment. Baur et al. (2006) studied if Resveratrol shifts the physiology of mice on a high-calorie diet towards that of mice on a standard diet. For this, male mice were fed either a standard diet or a high calorie diet. Additionally, mice from the high calorie diet were fed Resveratrol at two concentrations either on average 5.2mg/kg or 22.4mg/kg body weight. Effects in the higher dose group were more prominent; therefore Baur et al. (2006) presented in their study only the results for the higher dose. Baur et al. (2006) stressed that these doses are also feasible for humans. To assess quality of life in the Resveratrol group which showed increased survival; balance and motor co-ordination were assessed using a rotarod. On the rotarod it was measured how long it took before the mice fell from an accelerating rotating cylinder. Baur et al. (2006) demonstrated that the Resveratrol fed high calorie mice steadily improved their motor skills as they aged. Also of interest is that the rotarod performance improved with the Resveratrol fed mice on standard diet. Mitochondria are the principal energy source of the cell and play a significant role in performance and endurance, and also in many diseases (Baur at al., 2006; McArdle et al., 2010; Zoll et al, 2002; Jones&Carter, 2000). Baur et al. (2006) performed cell-based mitochondrial assays and found that Resveratrol treated mice had considerably more mitochondria in their livers compared to controls. Lagouge et al. (2006) also focused on mitochondria, but additionally this study assessed the activity of mitochondria. A focus was taken on peroxisome proliferator-activated receptor γ coactivator (PGC-1α) and muscle fibres, which both play an important role in endurance (McArdle et al., 2010; Zoll et al., 2002). Lagouge et al. (2006) had a similar approach to Baur et al. (2006), but this study used an up to 20 fold higher dose of Resveratrol for a shorter time and the control group had a high fat diet. Mice either received high fat diet or chow diet with a dose of Resveratrol of 200mg/kg or 400mg/kg body weight. Indirect calorimetry was used to measure energy expenditure. Basal energy expenditure was measured using oxygen consumption and was significantly increased in the Resveratrol fed mice (Lagouge et al, 2006). Ex-vivo muscle mitochondria analysis found in Resveratrol treated mice that mitochondrial activity was increased. Additionally, Lagouge et al.

Journal of Sport and Health Research 2013, 5(3):237-250

(2006) demonstrated that nonoxidative fibres in Resveratrol treated mice had larger and denser mitochondria aggregated between adjacent myofibrils, with increased activity of the mitochondrial enzymes citrate synthase and succinate dehydrogenase. Furthermore, this study showed that Resveratrol treated mice had a significantly higher maximum VO_2 rate, suggestive of an increased oxidative capacity. These findings are according to Lagouge et al. (2006) highly suggestive that Resveratrol increases the ratio of oxidative to non-oxidative type muscle fibres. Lagouge et al. (2006) evaluated the effect of Resveratrol in an endurance test to assess the effect on endurance. The results showed that high fat fed mice treated with Resveratrol run twice the distance until exhaustion than the high fat fed controls. As well as Baur et al. (2006), Lagouge et al. (2006) showed improved motor co-ordination and increased muscle strength in Resveratrol treated high fat diet mice. Furthermore, Lagouge et al. (2006) evaluated anxiety and sensorimotor function to discount for potential central nervous system mediated behavioural effects, with open field, light/dark box, maze test and hot-plate test.

In comparison to Baur et al. (2006) and Lagouge et al. (2006), Mayers et al. (2009) found that mice fed with a 0.1% Resveratrol diet performed worse on the treadmill than non Resveratrol treated mice after a 12 week exercise programme. Mayers et al. (2009) undertook his study to also evaluate if Resveratrol caused bradicardia or hypothermia like calorie restriction does. For this study Mayers et al. (2009) surgically implanted radio telemeters in free-moving mice. Compared to the calorie restricted mice which showed on the first day signs of bradicardia and hypothermia, the Resveratrol treated group did not show any signs after a week (Mayers et al., 2009).

The last of the animal studies adopted a different approach and wanted to find out if Resveratrol has an influence on the decline of physical performance, reduced endurance capacity and muscle force when you age. To test Resveratrol in combination with physical exercise in aging, Murase et al. (2009) used senescence-accelerated prone mice (SAMP) which show an accelerated aging process similar to humans. As a control group senescence-accelerated resistant mice (SAMR) were used. SAMP show over time impaired physical functions, higher oxidative stress, impaired mitochondrial function and shorter lifespan. Murase et al. (2009) examined the running endurance capacity of SAMP mice and SAMP mice fed with a 0.2% Resveratrol diet. Both groups underwent a 12 week daily exercise program on the treadmill. Running time until exhaustion for the SAMP without Resveratrol decreased over the 12 weeks, whereas Resveratrol-fed SAMP retained a significantly higher running time (35%). To clarify the effects of Resveratrol on physical function, Murase et al. (2009) looked at the force response to titanic stimulation of isolated soleus muscle, which showed that the combination of exercise and Resveratrol significantly increases muscle force (53%). Another interesting point in this study is that the Resveratrol treated group showed a significantly higher level of Haemoglobin (Murase et al., 2009). Of additional importance for endurance sports is the oxygen consumption which was significantly higher in the Resveratrol treated group, measured by indirect calorimetry (Murase et al., 2009). At the cell level Resveratrol treated SAMP mice showed higher levels of Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) and medium-chain acyl-CoA dehydrogenase (MCAD), which both play an important role in mitochondrial biogenesis and energy metabolism (Murase et al., 2009).

Journal of Sport and Health Research 2013, 5(3):237-250

The only human study with Resveratrol which is related to performance is a double-blind, placebo-controlled crossover study with 22 healthy participants assessing cognitive performance and localised cerebral blood flow (Kennedy et al., 2010). The participants received during 3 different visits 3 single dose treatments in an order by random allocation. The treatments were: 1) inert placebo 2) 250mg Resveratrol 3) 500mg Resveratrol. The participants were assessed using a collection of tasks to assess the effect of treatment on speed/accuracy and mental fatigue during continuous performance of cognitively demanding tasks (Kennedy et al., 2010). Cerebral blood flow was assessed by functional NIRS, which is a brain-imaging technique that is predicted on intrinsic optical absorption properties of oxygenated haemoglobin and deoxygenated haemoglobin (Kennedy et al., 2010). Kennedy et al. (2010) showed in his study that Resveratrol administration resulted in a dose-dependent increase in cerebral blood flow during task performance and enhanced oxygen extraction. Cognitive function was not affected.

Health and chronic medical problems

This section will present the results of the five studies in relevance to SEM, where Resveratrol in combination with exercise could have potential benefits for general health and chronic medical problems. Lagouge et al. (2006) showed in their study an induction of PGC-1α activity by facilitating SIRT-1 mediated deacetylation, which shows that Resveratrol is a potent SIRT1 activator. The activation of SIRT1 has multiple beneficial effects on health and chronic medical problems (see figure 1). Mayers et al. (2009) also showed that Resveratrol treatment up-regulated PGC-1α transcripts and acts therefore as a SIRT-1 activator. These finding have been showed to be present in brown adipose tissue, heart and liver tissue. Murase et al. (2009) showed a similar effect of Resveratrol. Resveratrol treatment in faster aging mice showed a suppression of the natural occurring decline of PGC-1α .

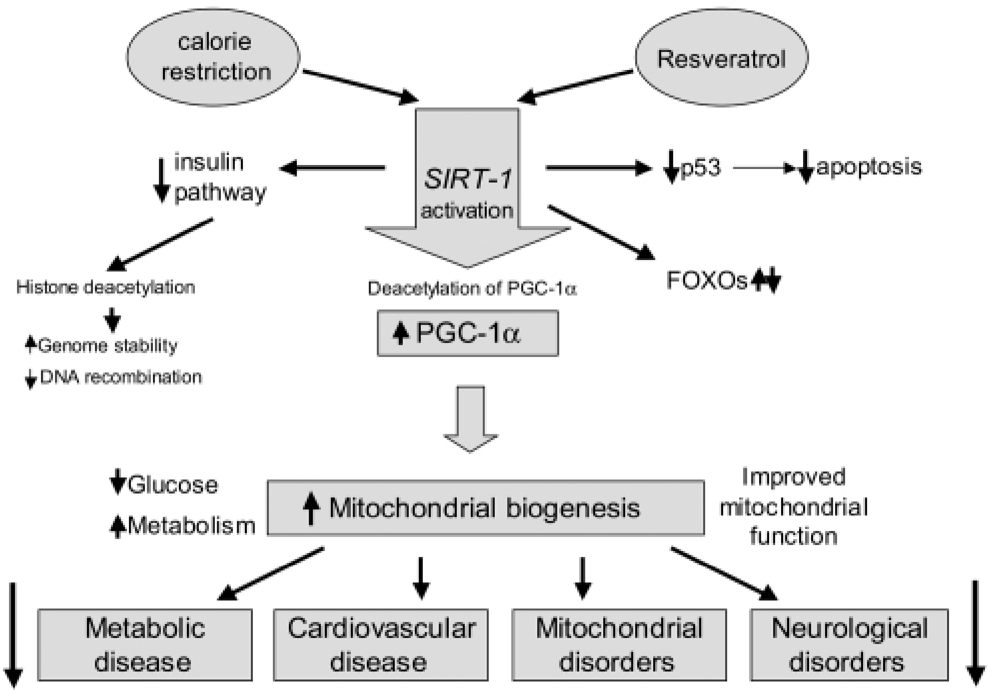

Figure 1: *SIRT-1* activation pathways. Resveratrol and calorie restriction activate similar *SIRT-1*–mediated pathways whose actions result in prevention of common age-related diseases. (Markus&Morris, 2008)

Baur et al. (2006) went one step further and showed that mice fed with a high fat diet had altered plasma levels of markers which predict onset of diabetes and a shorter lifespan, like insulin, glucose and insulin-like-growth factor-1. The Resveratrol fed group had significantly lower levels of these markers (Baur et al., 2006).

Murase et al. (2009) tested the physical decline in mice that age prematurely. One group had a combination of an exercise programme with Resveratrol and the other group only exercise. The findings of this study not only showed that the Resveratrol treated mice have a higher running capacity and muscle strength, but also showed that Resveratrol and exercise together influence markers of chronic medical problems. Levels of plasma insulin were reduced by 23% in the Resveratrol group, triglyceride concentration and plasma glucose levels were also significantly reduced in the exercise group treated with Resveratrol (Murase et al., 2009).

Journal of Sport and Health Research 2013, 5(3):237-250

Another known effect of aging is the tendency for increased body weight. Murase et al. (2009) showed that exercise and Resveratrol have a greater effect on body weight than exercise only. The body weight of Resveratrol treated mice was significantly lower (<8.5%) compared to exercise only (Murase et al., 2009).

Journal of Sport and Health Research 2013, 5(3):237-250

Table 2. Studies included in Literature review.

Study	Study design	Subjects	Intervention	Comparator	Outcome measures	Results
Baur et al. (2006)	Experimental animal study with in vivo and ex-vivo analysis	One year old male C57BL/6NIA mice	High calorie diet with fat High calorie diet with fat and resveratrol	Standard diet	Electron microscopy, cell based mitochondrial assays, Serum markers, AMPK and PGC-1α analysis, histology, Rotarod	Resveratrol group showed changes associated with longer lifespan, including insulin sensitivity, increased peroxisome proliferator receptor-coactivator 1α activity, increased mitochondrial number and improved motor function
Kennedy et al. (2010)	Double-blind, placebo controlled, cross over study	24 healthy adults, 4 men, 20 women, age range: 18-25	250mg Resveratrol + 500mg Resveratrol 45min before outcome measure	Inert placebo	Functional NIRS: brain-imaging technique that predicts the intrinsic optical absorption properties of oxygenated haemoglobin and deoxygenated haemoglobin, performance in cognitive tasks	Increase in deoxyhaemoglobin after both doses of resveratrol, which suggests enhanced oxygen extraction, cognitive function was not affected
Lagouge et al. (2006)	Experimental animal study, with in vivo and ex-vivo analysis	4 to 8 week male C57B1/6J mice	Resveratrol was mixed either with powdered chow or high fat diet	High fat diet without resveratrol	Body composition by DEXA indirect calorimetry, locomotor function by rotarod, string and grip test, glucose sensitivity, endurance test by variable speed belt treadmill and incremental speed protocol, O2 consumption, histological and biochemical analysis, including citrate synthase activity in gastrocnemius muscle, DNA RNA analysis, clinical genetic study	Treatment of mice with Resveratrol increased their aerobic capacity, evidenced by increased running time and consumption of oxygen in muscle fibres, increased PGC-1α activity, Resveratrol treatment protected mice against diet-induced-obesity and insulin resistance, SIRT1 as key regulator of energy and metabolic homeostasis

Journal of Sport and Health Research 2013, 5(3):237-250

Mayers et al. (2009)	Experimental animal study, with in vivo and ex-vivo analysis	Adult C57B1/6J mice, ob/ob mice, wild type mice	Mice on calorie-restricted diet (60% of their average food intake), Resveratrol group (feed containing 0.1% Resveratrol)	Mice fed ad libitum	Radiotelemetry (implanted electrocardiographic telemeters), Indirect calorimetry, Rotarod, Treadmill, RNA isolation	Short-or long-term Resveratrol has no effect on heart rate, body temperature or metabolic rate, Resveratrol treatment negatively affects endurance in mice, Resveratrol alters expression profiles in brown adipose, heart and liver tissues
Murase et al. (2009)	Experimental animal study, with in vivo and ex-vivo analysis	Male SAMP1 and SAMR1 mice	SAMP with normal diet and SAMP with normal diet supplemented with 0.2% Resveratrol for 13 weeks	SAMR strain as control as ages normally	A motorised rodent treadmill was used to determine the endurance capacity for running, Electrical muscle stimulation, Indirect calorimetry Blood analysis, RNA extraction and r-PCR	Endurance capacity of SAMP1 mice decreased over 12 weeks whereas SAMP1 mice fed 0.2% Resveratrol along with exercise remained significantly higher, SAMP1-Res also showed significant increase in oxygen consumption and skeletal muscle mRNA levels of mitochondrial function related enzymes

Journal of Sport and Health Research 2013, 5(3):237-250

DISCUSSION

The aim of this review was to evaluate the possible indications of Resveratrol in sports and exercise medicine. Based on the five studies reviewed, there is a variety of basic scientific findings which could make Resveratrol a valuable substance in sports and exercise medicine.

Finding a substance that could positively influence heart disease, cancer, diabetes and potentially extend life would be too good to be true. Enhancing performance and endurance capacity additionally into old age could help to lead to an active long life. According to an editorial in the journal Cell, Lagouge et al (2006) and Baur et al. (2006) brought this dream a bit closer (Koo et al., 2006). There is still one question to be answered: Are those effects reproducible in humans? And this question is the main critique for this review.

All four animal studies have their limitations towards assessing the suitability for sports and exercise medicine in humans as they are based on animal models. The potential for the treatment of several diseases has been recognised by several publications (Baur & Sinclair, 2006; Markus & Morris, 2008; Naylor, 2009; Das& Das, 2007; Martin et al., 2006; Koo et al. 2006). All four studies were conducted with a clear intervention and relevant control groups. All findings in each of the study have been statistically evaluated and have been significant compared to control group or additional interventions.

All four animal studies differ in the amount of Resveratrol used and the length of intake which possible could have an impact on the effects of Resveratrol (Koo et al., 2006). Mayers et al. (2009) study fed mice a 0.1% RSV diet for 12 weeks and could find no endurance enhancement. Murase et al. (2009) however found that the age related decline in endurance and performance in SAMP mice could be reduced with a 0.2% RSV diet for 12 weeks (Murase et al., 2009). This could mean that the performance enhancing effect of Resveratrol could be a dose dependent process. Looking at the Baur et al. (2006) and Lagouge et al. (2006) studies, which both showed an enhanced endurance performance, mice were fed either 22.4 mg or 200mg Resveratrol per kilogram body weight. Baur et al. (2006) also started his experiment with a dose 5.2 mg/kg, but saw more significant changes with the higher dose. A weak point in Mayers et al. (2009) study is that there is no mention of how much Resveratrol was fed per kilogram body weight, but in his discussion he mentions that the Resveratrol dose was between Baur et al. (2006) and Lagouge et al. (2006) dosage. Out of the four animal studies, three found a performance and endurance enhancing effect. But what could influence this as well as dose? The length of Resveratrol treatment seems also to be important. Although Lagouge et al. (2006) used 10 to 20-fold higher doses, the study fed Resveratrol over a shorter time compared to Baur et al. (2006). Baur et al. (2006) found that long term treatment (1 year plus) with a lower dose (22.4mg/kg) showed a remarkably improved insulin sensitivity and increased life span in mice fed a high fat diet. It is well known that exercise training transforms the metabolic status of myofibres to one of increased oxidative metabolism and switches the fibres from fast twitch type 2 to a slow twitch type 1 (Booth et al., 2002). Lagouge et al. (2006) showed in his study that Resveratrol treated mice on high-fat diets show a similar myofibre remodelling but in the absence of increased physical activity. Here the question arises if long term Resveratrol treatment with exercise could have a greater effect on transformation to slow twitch type 1 fibres and enhance endurance performance more than exercise alone. Comparable changes in muscle fibre types have been shown in genetically engineered mouse models that trigger or enhance PGC-1α activity (Lin et al., 2002). This means that Resveratrol could induce a muscle fibre type switch without the need for genetic engineering. Lagouge et al. (2006) see Resveratrol as a performance enhancing drug that improves performance by changing myofibre specificity rather than, like anabolic steroids, by increasing muscle mass. The authors also demonstrated that Resveratrol increases the size and content of mitochondria as well as the mitochondrial enzyme activity, which contributes to an increase in maximal oxygen consumption of those fibres (Lagouge et al., 2006). Resveratrol treatment also induced the expression of genes for oxidative phosphorylation and mitochondrial biogenesis (Lagouge et al., 2006). All these finding could be of immense importance for sports medicine and would need further evaluating in humans. But what is a safe and pharmacologically effective dose of Resveratrol to show these effects in humans? Pharmacologically

Journal of Sport and Health Research 2013, 5(3):237-250

relevant doses of Resveratrol have been established in animal studies from 22.4mg/kg body weight. Toxic effects in rats have been reported above 3000mg/kg body weight (Crowell et al., 2004). Important for the endurance enhancing effects might be long-term treatment with Resveratrol, but even long-term daily oral administration of above 1600mg for a 70kg person is regarded as safe (Juan et al., 2004; Crowell et al., 2004).

Physical performance is often dependent on cognitive performance and cognitive performance also has an influence in outcome in most sports and games. The only human study in this review with Resveratrol could show an increased cerebral blood flow, but no improvement in cognitive performance (Kennedy et al., 2010). It is well known that brain function is dependent on the delivery of blood borne metabolic substrates to active tissue. Kennedy et al. (2010) conducted placebo control double blinded investigation with 22 subjects, which showed that the consumption of Resveratrol resulted in a dose-dependent pattern of higher cerebral blood flow in the prefrontal cortex. Concentrations of deoxy-Hb were significantly higher after both doses of Resveratrol than after placebo, which is suggestive of an increase in oxygen extraction and utilisation (Kennedy et al., 2010). This supports the findings of Baur et al. (2006) and Lagouge et al. (2006) that Resveratrol has beneficial effects on mitochondrial function and biogenesis. Under discussion in many publications concerning Resveratrol and other polyphenols is low bioavailability of the parent molecules in humans (Baur & Sinclair, 2006, Markus & Morris, 2008). The relevance of much of the presented in vitro literature to oral consumption by humans has been questioned (Baur & Sinclair, 2006, Baur et al., 2006), but Kennedy's et al. (2010) results clearly show that orally administered Resveratrol can modulate brain function in humans and provide the first indication in humans that Resveratrol may be able to modulate cerebral blood flow variables.

As the number of overweight individuals worldwide has reached 2.1 billion, an explosion of obesity-related health problems like cardiovascular disease, diabetes, cancer and inflammatory disorders has been seen. Baur et al. (2006) conducted his study to see if Resveratrol could improve health in a high fat diet in mice to possibly counteract obesity related health problems. The results are promising and show that Resveratrol produces changes associated with a longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 levels, increased PGC-1α activity, increased mitochondrial number and improved motor functions (Baur et al., 2006). Lagouge et al. (2006) even found that short term (15 weeks) Resveratrol treatment protected young male mice against obesity induced by a high-fat diet. Amounts of adipose tissue were significantly reduced in these mice, due in part to increased fat burning by mitochondria-enriched brown adipose tissue. The question for exercise medicine is does Resveratrol and exercise together give a greater effect on insulin sensitivity and weight than exercise alone? The reviewed study of Murase et al. (2009) in faster aging mice hints that there might be a synergistic effect of Resveratrol and exercise. The findings suggest that the energy metabolism-activating effect of combined Resveratrol intake and habitual exercise might contribute to suppressing obesity. It has been shown that average body weight of SAMP mice fed Resveratrol was significantly lower than that of SAMP controls (Murase et al., 2009). Additionally, levels of insulin, glucose and triglycerides were reduced in the Resveratrol group, which may contribute to prevent diabetes, hyperlipidemia and atherosclerosis (Murase et al., 2009). These finding suggest that Resveratrol together with exercise could provide greater health benefits that exercise only. Another significant finding in Murase's et al. (2009) study was that the decline of muscle force and performance was reduced in the Resveratrol group. These findings and the findings of Baur et al. (2006) and Lagouge et al. (2006) of an improved motor function in Resveratrol treated mice could also mean that older people could stay active longer and benefit from the positive health effects of exercise for longer.

There are no established doses for resveratrol but Kennedy et al. (2010) showed in humans that resveratrol administration with doses of 250 mg and 500 mg, resulted in a dose-dependent increase in cerebral blood flow during task performance and enhanced oxygen extraction. Doses of 1600 mg per day in a 70 kg participant are regarded as safe even long term (Juan et al., 2002).

Journal of Sport and Health Research 2013, 5(3):237-250

IMPLICATIONS FOR FURTHER RESEARCH

This review has highlighted the potential of several possible indications for Resveratrol in sports and exercise medicine. There is clearly a need to conduct human studies to verify the findings of the presented animal studies. As the amount and the length of Resveratrol intake seems to influence outcome, special focus should be taken when conducting research in humans. Doses between 22.4mg/kg and 200mg/kg Resveratrol for longer than 15 months seem to be safe in humans (Baur & Sinclair, 2006; Markus & Morris, 2008;, Crowell et al., 2004; Juan et al., 2002; Crowell et al., 2004). Outcome measures which could be of interest for the competing athlete could be a potential performance enhancement of endurance sports, but also the effect on sports with a degree of higher coordination tasks should be examined. The possible effects of the anti-inflammatory potentials of Resveratrol on exercise related injuries or rehabilitation was not evaluated in this review, but could also lead to further research in the area of sports medicine.

Looking especially at the results of Murase et al. (2009), human studies are clearly needed to evaluate if Resveratrol treatment and exercise together can reduce obesity and have positive influence on factors related to developing chronic diseases like heart disease, diabetes or cancer.

As a final thought on further research, the aging associated decrease in performance and muscle function would be of significant interest related to the SEM health and performance continuum.

CONCLUSIONS

In this review a systematic approach has been taken within strict selection criteria to assess the body of literature to evaluate the potential indications of Resveratrol in sports and exercise medicine. The basic research presented in this review leads to the conclusion that Resveratrol as a food supplement in sports and exercise medicine has not had much attention in human research. Animal studies so far have shown benefits of Resveratrol intake to enhance endurance performance in mice (Baur et al., 2006; Lagouge et al., 2006) and suppressing the aging-related decline in physical performance (Murase et al., 2009). Basic research on the metabolic level shows that Resveratrol on its own and in conjunction with exercise have a positive influence on changes associated with longer lifespan and in chronic medical conditions (Baur & Sinclair, 2006; Markus & Morris, 2008; Baur et al., 2006; Lagouge et al., 2006;Murase et al., 2009).

In conclusion, the reviewed research so far suggests Resveratrol has enormous potential for the use in high performance sports as well as to enhance the health benefits of exercise for the general population, particularly to decrease a number of obesity or age related diseases and complications.

REFERENCES

1. Baur, J. A., Sinclair, D. A. (2006) Therapeutic potential of resveratrol: the in vivo evidence. *Nature.* 5: 493-506.
2. Baur, J. A., Pearson, K. J., Price, N. L., Jamieson, H. A., Lerin, C., Kalra, A., Prabhu, V. V., Allard, J. S., Lopez-Lluch, G., Lewis, K., Pistell, P. J., Poosala, S., Becker, K. G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K. W., Spencer, R. G., Lakatta, E. G., LeCouteur, D., Shaw, R. J., Navas, P., Puigserver, P., Ingram, D. K., de Cabo, R., Sinclair, D. A. (2006). Resveratrol improves health and survival of mice on a high-calorie diet. *Nature.* 444: 337-342.
3. Booth, F. W., Chakravarthy, M. V., Spangenburg, E. E. (2002). Exercise and gene expression: physiological regulation of the human genome through physical activity. *J. Physiol.* 543: 399–411.
4. Crowell, J. A., Korytko, P. J., Morrissey, R. L., Booth, T. D., Levine, B. S. (2004). Resveratrol-Associated Renal Toxicity. *Toxocological Sciences.* 82: 614-619.
5. Das, S. & Das, D. K. (2007). Anti-inflammatory responses of resveratrol. *Inflammatory Allergy Drug Targets.*6(3): 168-173.
6. Jackson, J. R. (2009). Resveratrol Preserves Muscles Mass, Force Output and Mediates Oxidative Stress in Gastrocnemius Muscles from Hindlimb Suspended Rats. *Medicine&Science in Sports&Exercise.* 41(5): 136.
7. Jones, M. A., Carter, H. (2000). The Effect of Endurance Training on Parameters of Aerobic Fitness. *Sports Med.* 29(6): 373-386

8. Juan, M. E., Vinardell, M. P., Planas, J. M. (2002). The Daily Oral Administration of High Doses of *trans*-Resveratrol to Rats for 28 Days Is Not Harmful. *The Journal Nutrition.* 132:257-260.

9. Kennedy, D. O., Wightman, E. L., Ready, J. L., Lietz, G., Okello, E. J., Wilde, A., Haskell, C. F. (2010). Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation. *Am J Clin Nutr.* Mar 31. [Epub ahead of print].

10. Koo, S-H. & Montminy, M. (2006). Leading Edge: In Vino Veritas: A Tale of Two Sirt1s? *Cell.* 15; 127(6): 1091-1093.

11. Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., et al. (2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell.* 127: 1109-1122.

12. Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., Michael, L. F., Puigserver, P., Isotani, E., Olson, E. N. (2002). Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature*. 418: 797–801.

13. Markus, A., Morris, B. J. (2008). Resveratrol in prevention and treatment of common clinical conditions of aging. *Clinical Interventions in Aging.* 2: 331-339.

14. Martin, A. R., Villegas, I., Sanchez-Hidalgo, M., de la Lastra, C. A. (2006). The effects of resveratrol, a phytoalexin derived from red wines, on chronic inflammation in an experimentally induced colitis model *British Journal of Pharmacology.* 147: 873-885.

15. Mayers, J. R., Iliff, B. W., Swoap, S. J. (2009) Resveratrol treatment in mice does not elicit the bradycardia and hypothermia associated with calorie restriction. *The FASEB Journal.* 23: 1032-1040.

16. McArdle, W. D., Katch, F. I., Katch, V. L. (2010). *Exercise Physiology* (7th Edition) Baltimore: Lippincott, Williams&Wilkins.

17. McCrory, P. (2006). What is sports and exercise medicine. *Br J Sports Med.*40: 955-957.

18. Murase, T., Haramizu, S., Ota, N., Hase, T. (2009). Suppression of the aging-associated decline in physical performance by a combination of resveratrol intake and habitual exercise in senescence-accelerated mice. *Biogerontology.*10: 423-434.

19. Naylor, A. J. D. (2009). Cellular effects of resveratrol in skeletal muscle. *Life Sciences.* 84: 637-640.

20. Zoll, J., Sanchez, H., N'Guessan, B., Ribera, F., Lampert, E., Bigard, X., Serrurier, B., Fortin, D., Geny, B., Veksler, V., Ventura-Clapier, R., Mettauer, B. (2002). Physical activity changes the regulation of mitochondrial respiration in human skeletal muscle. *Journal of Physiology.*543(1):191-200.