Eco Salt
ALL NATURAL
SALT SUBSTITUTE

Nitric oxide, endothelium and cardiovascular function

The endothelium is an organ widely distributed throughout the organism, with an approximate weight of 1.5 kg, it is deeply involved in multiple functions synthesizing, metabolizing and releasing a number of substances that exercise effects acting in autocrine, paracrine, or epicrine modes. (Bassenge, 1996). Amongst these substances the NO is of utmost importance, because of its fundamental role in several endothelial functions, such as the regulation of the vessel-motor tone, the inhibition of platelets activity, the keeping of the balance between the processes of thrombosis and fibrinosis and the regulation of the recruitment of inflammatory cells inside the vascular wall (Vallance and Collier, 1994; Court et al. 2002).
As explained, the NO and other endothelial factors are continuously synthesized and released at a level called “basic”; additionally can be released in greater amounts as consequence of the action of local or circulating ‘triggers’ (bradikine, serotonine, norepinefrine), through a process of biochemical and endocrine communication; additionally the endothelium responds to hemodynamic signals, as the increase of rub stress produced by the rise in the blood flow speed; this effect is observed, for example, during the performance of exercise, inducing acute and chronic changes in the production and release of NO (Lamontagne et al. 1992; Nishida et al. 1992), that we shall discuss further on.
The alteration of endothelium normal function has been denominated ‘endothelial dysfunction’ and is clearly associated with arterial hypertension and atherosclerosis, and has been implicated in other pathologies such as myocardial ischemia in patients with stable coronary disease, in the unstable coronary syndrome (López-Jaramillo et al. 1995), and in diabetes mellitus (Wu et al. 1995). It has been also demonstrated that, in absence of intact endothelial function, or even during normal aging process, the capacity of synthesizing and releasing NO and other endothelial autacoids is reduced, and in consequence the capacity of vessel dilation in the arteries is diminished.
It is known that blood pressure increase, whether acute or chronic produce, amongst other: endothelial damage an morphological changes in the arterial inside (Luscher and Noll, 1995); during chronic hypertension the endothelium grows into the light and the subendothelial space thickens. This might cause the reduction of access to the derivate NO from the endothelium to the flat vessel muscle, which might, in time, cause greater hypertrophy and hypertension (Berrazueta, 1995). Whether the endothelial damage is a primary or secondary phenomenon, it is clear that it aggravates the vessel anomalies and contributes distinctively in the pathogenesis of hypertension.
Experiments in which the interference with the synthesis or action of the NO will cause an increase of blood pressure in animals (Breslow et al. 1993; Brady et al. 2002) or in humans (Gardiner et al. 1990; Vallance, 1998; Huynh and Tayek, 2002) are already classic. The chronic inhibition of NO production will quickly conduce to all the organic consequences of a severe arterial hypertension,

with atherosclerosis and loss of vessels in the Central Nervous Sysistem and kidneys (Moncada et al. 1991; Calver et al. 1993; Moncada and Higgs, 1993).
Clinically it has been demonstrated that there are lower levels of NO in patients with normal tension

that are children of hypertensive individuals (Taddei et al. 1996). This suggest that some step of the synthesis and release process of the NO would be genetically regulated, explaining the cause of greater cardiac risk in patients with family hypertension. On the other hand, arterial hypertension it is associated with other risk factors, such as dyslipidemia (MacMahon et al. 1985), hyperinsulinemia (Hanson et al. 2002) and sensibility to salt (Weinberger, 1991).

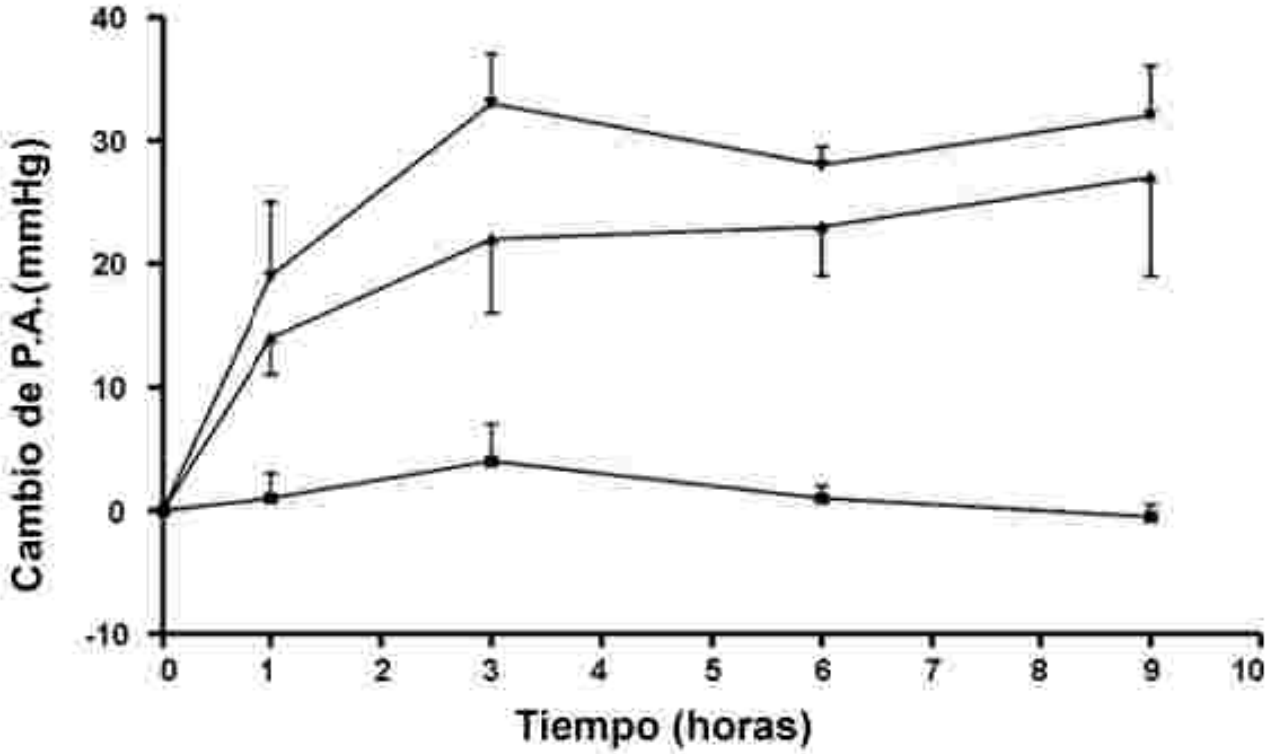

Figura 5
La presión arterial de animales aumenta de manera dosis dependiente al recibir un inhibidor de la síntesis de NO.

It is important to point out that most of the risk factors, like the abovementioned , produce no singular symptoms amongst the patients that suffer them, which make their early diagnose difficult. This is why it is necessary to inform and educate the general population about the importance of prevention, early detection and suitable treatment of the risk factors that have a role in developing a cardiac or metabolic disease. With this aim, amongst others, the 'Center for early detection and treatment of silent factors of cardiovascular and metabolic disease' (SIL-DETECT) at the clinical pharmacology unit, in the pharmacy faculty, at the Universidad Central de Venezuela. Amongst the objectives of the study, it is to determine the proportion of patients which arterial pressure suffers changes according to their intake of salt (salt sensibility) in a

population of apparently healthy Venezuelan adults, and study, in those patients, the possible connection between salt sensibility and the production of NO. The results of this study will be addressed further on.

Blood pressure shifting in connection with salt intake: the role of NO

Salt, an invisible killer.

When we eat more salt tan we need there is a great risk of blood pressure increase…
It is statistically demonstrated that the main death causes in developed countries have to do with cardiac diseases. One of its causes is the silent arterial hypertension.
It is silent because on the majority of cases there is hardly any symptom. People that suffer it don't complain from any ailment and therefore, do not consult with the doctor.
According to WHO, human organism daily sodium needs are approximately around six grams only, including the salt already provided in aliments.
Table salt has two components: chlorine and sodium, the latter being a key element for our health, because of its higroschopic properties, which means it can retain water.
It is almost unfeasible to abolish salt, but when establishing a diet, it is necessary to take into account the amounts included in natural aliments. A 60% of daily consumption of sodium chloride comes from the so called "invisible salt" which can be found in not salty aliments like cereals, cookies, tinned food or ketchup. Meat, for example, contains 65 mg of salt in 100 g, the egg 122 mg., fish 140 mg. in a 100 g, and a slice of bread contains 114 mg.
As has been stated by Hector Carrasco, Doctor in Chemistry, and lecturer in the Universidad Andrés Bello (Chile), sodium hides in a number of aliments which are not salty, like cheese, meat, cookies, cereals and vegetables. Other sodium composites apart from salt are involved in the industrial processing of the aliments, to better the taste, as conservatives or to bleach fresh products. He also explains that some aliments posses a really high level of salt: cold meats, tinned food, sausages, fried potatoes, snacks, peanuts, butter, hamburgers, frozen products, bakery products, baking powder, mayonnaise, ketchup, mustard, mineral water and sodas, amongst others. Many "light" aliments are not diet: they may be low fat, but filled with sodium. It is estimated that 60% of our daily consumption of sodium comes from the so called, "invisible salt", warns doctor Carrasco.
In contrast, low sodium diets are related with normal blood pressure, considerably diminishing associated risk like cardiac diseases and strokes.

Determination of salt sensibility:

The patients were under a seven day intake of high sodium (200mEq/day). During the following seven days, they followed a diet highly restricted in sodium (20-40mEq/day). Before starting the diet and in the seventh day of both diets, the patients went back to the Center for the following procedures: measurement of systolic blood pressure, measurement of diastolic blood pressure, heart frequency, 24-hour urine for quantification of nitrates and nitrites and urinary creatinine. The following of the high or low intake was checked by quantifying the urinary sodium at the end of every seven day period.
According to the changes in blood pressure figures obtained after the high or restrictive intake of salt, the patients were classified as salt sensitive or salt resistant, in terms with the abovementioned criteria. Of the studied population 23 resulted salt sensitive and 25 resulted salt resistant. The rest of the patients were classified as salt intermediate, with shifts in their blood pressure that oscillated between 4 and 9mmHg, when changing from a high salt to a low salt diet.

Figura 6

Representación esquematica de la prueba de Sensibilidad a la sal
Los sujetos siguen durante 7 días a una dieta con alto contenido de sodio (200 mEq/día). A continuación, y durante los siguientes 7 días, siguen una dieta con restricción severa de sodio (20-40 mEq/día). Los cambios de PAM entre las dietas alta y baja en sodio permite clasificar a sujeto en Sal-Sensible (>10 mm Hg) o Sal-Resistente (<3 mm Hg).

Quantification of nitrites and nitrates:

We used the Phizackerly Dabbagh (1983) method, modified in our laboratory. Briefly, the day of the trial the proteins present in the urine samples were precipitated with ZnSO4. Afterwards, the urinary nitrates are transformed into nitrites through chemical reduction with cadmium pearls. Once all the nitrates are transformed into nitrites they are quantified by spectrophotometric at 540nm, using the Griess reactive agent.
In the population of healthy patients studied, 26% turned out to be salt sensitive; 28% turned out salt resistant; the rest (46%) had an intermediate sensibility to salt. It is important to point out that salt sensitive patients were older, heavier and had a greater tendency to a higher waist-hip rate. Also they had a higher original blood pressure.

Sal sensibles Sal resistentes
Edad (Años) 46.7± 2.1** 38.2 ± 1.9
Peso (Kg) 79.1± 3.0 ** 71.7± 2.6
IMC (Kg/m$_2$) 31 ± 1.0 * 26.6 ± 0.8
RCC 0.94 ± 0.02 * 0.88 ± 0.02
PAS (mmHg) 131 ± 3.9 ** 111 ± 2.2
PAD (mmHg) 84.3 ± 2.6 ** 75 ± 1.4
PAM (mmHg) 100 ± 2.7 ** 87.1 ± 1.6
Ins ayunas (uUI-ml) 21.1 ± 2.6 22.6 ± 3.0
Ins 2hrs (uUI-ml) 126.8 ± 17.4 116.2 ± 15.5
Glu ayunas (mg/dl) 94.2 ± 4.3 88 ± 2.7
Glu 2 hrs (mg/dl) 125 ± 10.1 104.3 ± 6.1

Amongst the salt sensitive patients, the blood pressure diminished significantly and the excretion of metabolites of NO increased significantly, when they were under the low salt diet. In these patients the urinary excretion of metabolites of NO during the high salt diet was 45% lower than the excretion during the low salt diet. Amongst the salt resistant patients, the shifts in the intake of salt was not associated with any blood pressure shifts or the urinary excretion of NO metabolites.

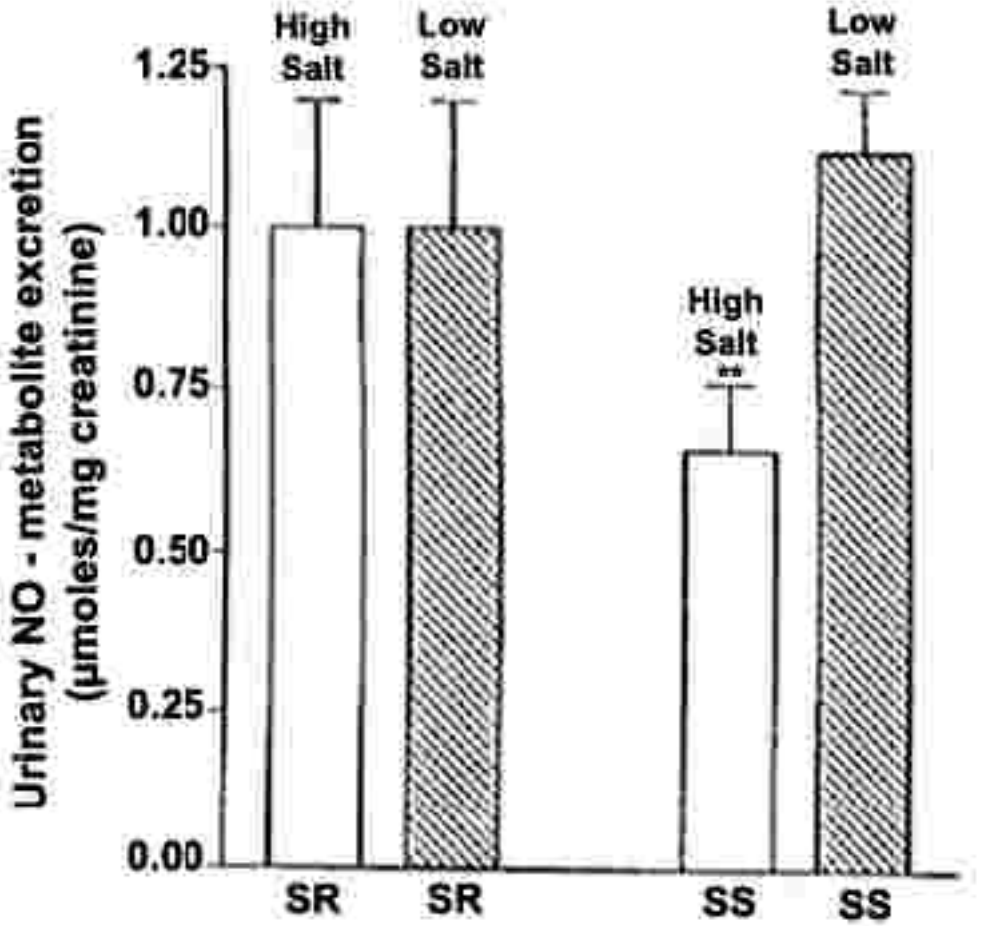

Figura 7
Cambios en la excreción urinaria de metabolitos del NO, en sujetos Sal-Sensibles (SS) y Sal-Resistentes (SR), después de una semana de ingesta alta o baja en sal (Cubecdu y col., 2000)

The results of this study enabled us to conclude that the salt intake does not modify the urinary excretion of No metabolites in the salt resistant patients, while it does significantly amongst the salt sensitive patients, who excrete lower levels of urinary metabolites of NO during the high salt diet. When going from a high salt intake into a low salt intake, the salt sensitive patients increase the production of NO, suggesting that in those patiente the high salt (or the increase in blood pressure caused by the high salt) reversibly stops the production of NO, which is corrected (same as blood pressure) when reducing the intake of salt. Additionally, these results, together with other related evidence (Fujiwara et al. 1998) allowed us to suggest that there is an important interaction between hyperinsulinemia, hyperglycemia, endothelial dysfunction and salt sensibility, and though several theories have been put forward to explain this relationship, currently, the precise physiopathologic mechanism by which these associations occur and the sequence of them is still unknown. Some studies point out that acute hyperinsulinemia delivers a strong antiatriuretic effect (De Fronzo et al. 1975) which continues still during the chronic hyperinsulinemia associated with obesity, despite the peripheral resistanceof the tissues to the action of insulin (Rocchini, 1994). In this case, the role of NO in the nephric modulation of the sodium handling is determining; the mechanism of NO production increase by increasing the sodium amount in the organism would be the direct mode to ease the sodium excretion; this hability seems to be altered in salt sensitive patients . With the end to contribute to the clearing up of some of the unknown factors in this area, at SIL-DETECT there are several continuing studies about cardiovascular risk factors with special emphasis in hiperinsulinism, salt sensibility and endothelial disfunction.