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Taurine's Role in Cellular Longevity: Implications for Aging and Senescence

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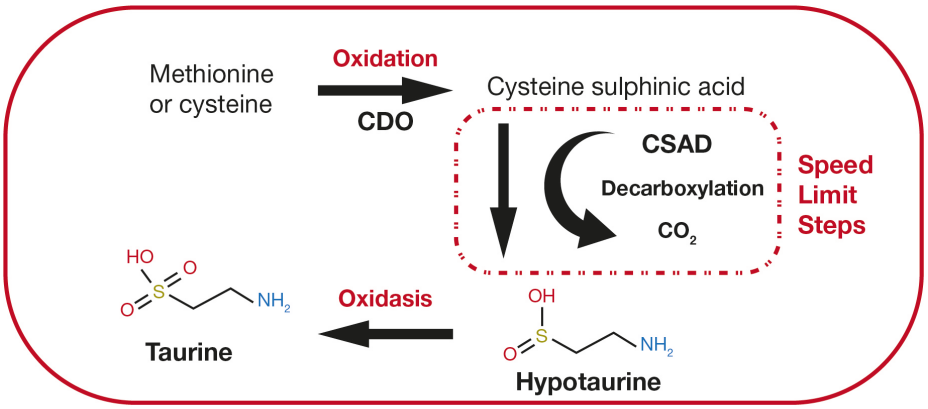
1. Introduction

Taurine is one of the most abundant amino acids found in organisms across eukaryotic phyla. Unlike most amino acids, taurine is not metabolized or incorporated into protein; instead, it serves several critical roles in various physiological processes including osmoregulation, antioxidant activity and membrane stabilization [1]

Taurine is either synthetized in cells from cysteine (Figure 1) or taken in with food. Intracellular taurine level is under the control of a taurine transporter (TauT) involved in the gating of taurine across the cell membrane and regulated by PKC phosphorylation at the post-translational level [2].



CDO: Cysteine DiOxygenase - **CSAD**: Cysteine Sulphinic Acid Decarboxylase

Figure 1 : Taurine synthesis

Taurine in its native form and when transformed in taurine chloramine exerts strong antioxidant and anti-inflammatory activity; it protects against UVB-induced skin inflammation by promoting the expression of Nrf2 mediated antioxidant / anti-inflammatory enzyme and suppress pro-inflammatory gene expression [3].

Taurine deficiency may contribute to aging, with supplementation showing promise in improving longevity and health in mammals. Taurine molecule is able to target nearly all hallmarks of aging: genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis,

nutrient-sensing, mitochondrial dysfunction, stem cell exhaustion, intercellular communication, inflammation and cellular senescence [4] (Fig. 2).

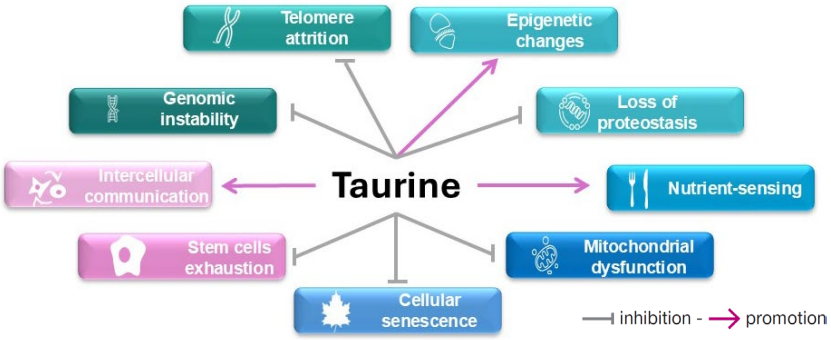


Figure 2: Taurine effects on key hallmarks of aging

A recent publication in Science journal, evoked that even taurine concentration was said to decline with age, a reversal of this decline through taurine supplementation was shown to increase life span and health span on mice and worms [4]. However, these observations have not yet been confirmed on humans.

The aim of our study was therefore to confirm taurine activity on longevity on human skin cells.

2. Materials and Methods

Taurine and Taut receptor

Evolution of taurine and TauT receptor were observed *in vitro* on keratinocytes.

Human epidermal keratinocyte cells were obtained from a 39-year-old donor. They were cultivated in keratinocyte medium until confluency at 37°C and 5% of CO_2. Cells were incubated during 24 hours in absence or in presence of the tested compound diluted directly in incubation medium. Culture medium was used as untreated control. Phorbol myristate acetate (PMA), a protein kinase activator was used as positive control (10ng/mL).

At the end of the incubation period, intracellular taurine and Taut content were quantified in cell lysates, obtained by sonication, using a specific ELISA kit. At the end of the incubation period, the protein level in the cell lysates was also quantified using a Spectrocolorimetric method (Bradford method). The results were expressed in percentage of taurine and TauT normalized at the level of cellular proteins compared to the untreated control set at 100%.

Results are expressed as Mean value ± SD (n=3) compared to untreated control set as 100%

The statistics were performed according to SigmaPlot software (V12.5) (Systat Software Inc. San Jose, California United States of America). Statistical analysis was assessed by One Way Anova test vs untreated control with threshold of significance set to 5% ($p<0.05$).

p21 expression

Taurine effect was also evaluated *in vitro* on p21 a cyclin dependent kinases (CDK) marker of cell cycle arrest.

Normal human dermal fibroblasts obtained from abdominal biopsies from a 34-year-old woman donor, were cultured in monolayers and grown to confluence in 12 well-plates in fibroblast growth medium added with 10% fetal calf serum, Glucose, L-glutamine and antibiotics for 96 hours at 37°C/5% CO2. Confluent fibroblasts in defined fibroblast growth medium (reference du milieu) were treated with Taurine (T8691). NaBu (Sodium Butyrate, B5887) was used as stress inducer to induce senescence and to impact p21 protein level production.

Taurine was tested at 12.5 and 25 mM into the culture medium.

At confluence, cells were treated, or not (untreated control, UC), 48 hours at 37°C and 5% CO_2 in the presence of NaBu with or without Taurine.

After treatment, the cells were harvested and lysed. Protein concentration was determined by bicinchoninic acid (BCA) assay, and the samples were adjusted at the same concentration of proteins. p21 protein was quantified using Western-Blot analysis system (Sally Sue: Protein-Simple. San Jose. California. USA) with primary antibody against p21 (NBP2-44525) and a horseradish peroxidase-conjugated secondary antibody (042-205 from Bio-Techne) detected by chemiluminescent substrate (from Bio-Techne). The resulting chemiluminescent signal was detected and quantified by the Compass Software version 2.7.1 (ProteinSimple. San Jose. California. USA).

p21 expression level was expressed as mean percentage ± standard deviation (n=3) compared to the NaBu control. Statistical analysis was assessed by One Way Anova test with threshold of significance set to 5% ($p<0.05$).

SASPs: IL-6 and IL-8

Normal human dermal fibroblasts obtained from 34-year-old donor were cultured in monolayers and grown to confluence in defined fibroblast growth medium with antibiotics at 37°C/5% CO_2.

Sodium Butyrate (NaBu) was used as senescence inducer. Cells were treated 24h with the Taurine, then treated 48 hours with NaBu 20mM and Taurine. Culture medium with NaBu was used as control (NaBu control).

IL-6 and IL-8 were quantified on cell culture supernatant with specific ELISA kit from R&D Systems (USA) with quantitative sandwich enzyme immunoassay technique. Monoclonal antibody specific for human IL-6 and IL-8 were pre-coated onto a microplate. Standards and samples were pipetted into the wells and any IL-6 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human IL-6 or IL-8 are added to the wells. Following a wash to remove any unbound

antibody-enzyme reagent, a substrate solution was added to the wells and color develops in proportion to the amount of IL-6 bound in the initial step. The color development was stopped, and the intensity of the color was measured.

Results are expressed as Mean value ± SEM (n=3) compared to the NaBu control set as 100%.

The statistics were performed according to SigmaPlot software (V12.5) (Systat Software Inc. San Jose, California United States of America).

Statistical analysis was assessed by One Way Anova test with threshold of significance set to 5% ($p<0.05$).

3. Results

PMA was shown to increase intracellular Taurine content and TauT receptor by 144% and by 193% ($p<0.001$) in human skin keratinocytes (Fig 3) demonstrating that these targets could be induced in human skin cells.

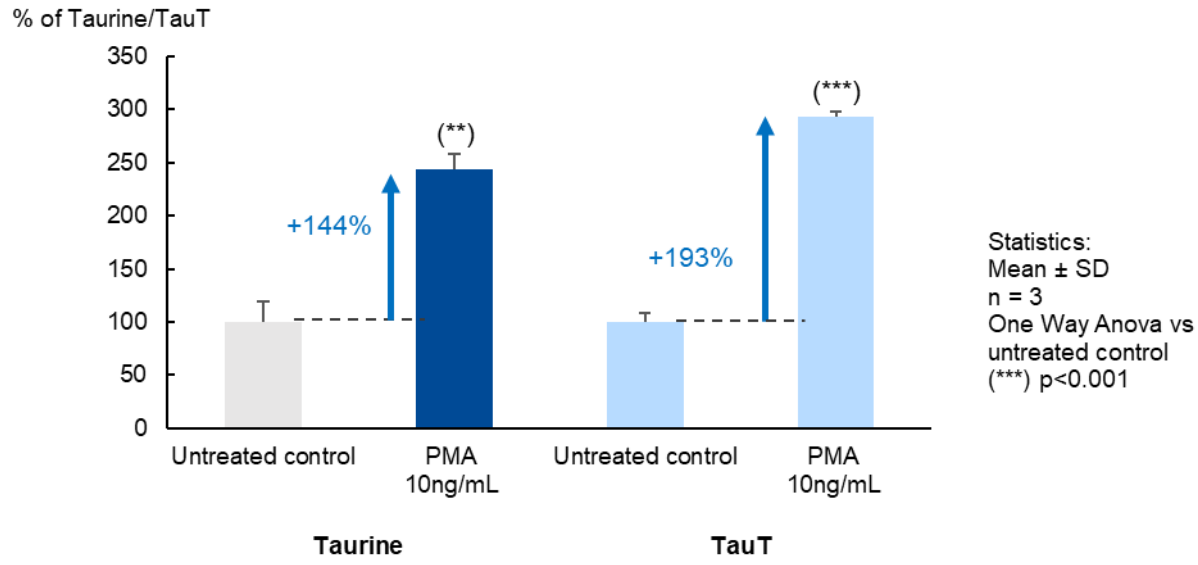


Figure 3. Intracellular quantification of taurine and Taut in keratinocytes after application of phorbol myristate acetate (PMA), a protein kinase activator.

Taurine was able to counteract the increase of p21 by sodium butyrate, by up to 42% ($p<0.05$) in human skin fibroblasts, indicating the important role of taurine in human skin cell senescence (Fig 4).

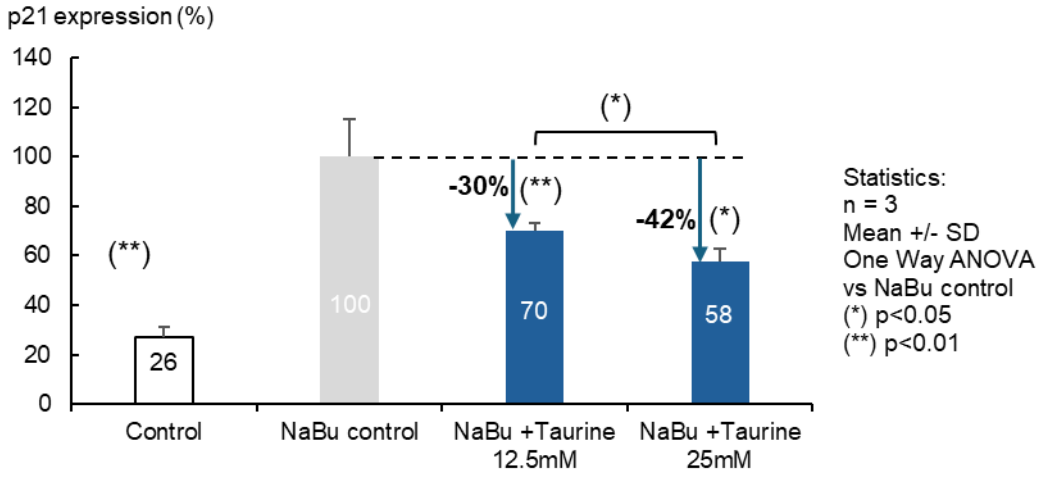


Figure 4. Evolution of p21 expression after application of sodium butyrate (NaBu) in human skin fibroblasts.

Similarly, taurine was able to reverse the increase of Il-6 and IL-8 expression by up to 45 ($p<0.001$) and 69% ($p<0.001$) respectively (data not shown).

4. Discussion

Taurine molecule is able to target and inhibit several hallmarks of aging including cellular senescence. In mammal, supplementation with taurine showed promising effect on health and longevity [4]. Furthermore, taurine and its transporter have been shown to be present in epidermis [Siefken et al, 2003].

In our study, we observed that Phorbol Myristate Acetate (PMA) was able to increase taurine and its transporter in skin cells confirming the importance of taurine in mammal cells.

We also confirmed the role of taurine in the senescence regulation via the modification of p21 expression, and its influence on senescence associated skin phenotypes (SASP) such as Il-6 and Il-8 on skin fibroblasts in a NaBu-senescent induced model.

These observations first showed the antisenescence benefits of taurine for human cells. Then, the models developed for this study may be useful to select active ingredients that can modulate taurine and its transporter TauT essential for its bioavailability. Focusing on the Taurine amino acid and its transporter to reach a high intracellular concentration of taurine could represent a novel approach to achieving an effective anti-senescence effect, as evidenced by a reduction in the levels of the senescence-associated secretory phenotype (SASP).

5. Conclusion

Aging is no longer an enemy to fight but a process to embrace. Beauty now focuses on extending the lifespan of the skin, by shifting to combating visible signs of aging toward a more holistic approach centered around rebuilding skin health and vitality at every level.

Interestingly, recent studies highlighted taurine's potential in slowing aging and extending health span but was not studied for humans. In our study, we demonstrated the important role of taurine and its transporter TauT in skin cells suggesting it could thus pave the way for new strategies to fights against skin senescence.

6. References

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