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Abstracts

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01.021 **Pioglitazone Combined with Cold Exposure Increase Proteasome Activity and Modulate Intracellular Peptides Profile in Adipose Tissues.** Valdivia LFG¹, Jardim GFR², Moreira RJ², Ferro ES³, Reckziegel P^{1,2} ¹Unifesp, PPG Pharmacology; ²FCF-USP, Dpt of Clinical and Toxicological Analysis ³ICB-USP, Dpt of Pharmacology

Background: Intracellular peptides (InPeps) primarily originate from proteasomal protein degradation and evade further degradation by oligopeptidases and peptidases, thus not being reduced to amino acids. Some InPeps have been associated with reduction of white adipose tissue (WAT) mass, and lowering glucose levels and liver fat in obese rodents. The InPeps content and the activity of the protein degradation apparatus during the thermogenic process have not yet been investigated in brown adipose tissue (BAT) and WAT of mice. **Aim.** This study aimed to investigate the InPeps profile during the activation of BAT and WAT, and to correlate it with proteasome activity and secondary protein degradation (i.e. InPeps profile). **Methods:** Male C57BL/6 mice (CEUA-ICB/USP, #8874310719) were treated with either water (control) or pioglitazone (30mg/kg/day), and exposed to 21°C or 7°C (cold) for 15 days. Interscapular BAT (iBAT) and inguinal WAT (iWAT) were processed for peptidomics, proteasome activity and gene expression analysis. Statistical analyses were performed by two-way ANOVA and Tukey's test ($P < 0.05$). **Results:** Cold exposure led to relative increased levels of InPeps both in iBAT and iWAT (vs. Control). Conversely, Pio+Cold group showed relative decreased levels of InPeps compared to the control untreated group (the results of peptidomics are expressed as relative abundance). However, the Pio+Cold group exhibited a twofold increase in proteasomal trypsin-like and chymotrypsin-like activities in BAT compared to the Control group ($P = 0,0002$ and $P = 0,0182$, respectively), and twofold increase in caspase-like activity in iWAT (vs. Control, $P = 0,0064$). The Pio+Cold also showed elevated gene expression of proteasome catalytic subunit (PSMB5) compared to all other groups analyzed and major oligopeptidases and peptidases, such as thimet oligopeptidase (2x on iBAT), neprilysin (2x on iBAT and 3x on iWAT), neurolysin (2x) and insulin-degrading enzyme (3x) in iWAT. **Conclusion:** This study highlighted the modulation of InPeps in pharmacological models of iBAT and iWAT activation, emphasizing the role of the proteasome and peptidases in these tissues. Despite the modulation in the quantity of intracellular peptides in Cold and Pio+Cold groups, the proteasome in Pio+Cold animals was more active, as were most of the analyzed peptidase genes. Apparently, the combination of treatments induces a more catabolic effect on the proteasome than when they are administered individually. Further analyses should address the role of cold in modulating InPeps generation, as well as to elucidate the function of InPeps in BAT and WAT. **Financial Support:** São Paulo Research Foundation (FAPESP processes #2019/25943-1, 2021/03717-0 and 2023/02579-8).