# Functional and molecular interplay between *PPARα* receptors and *TRPV1* channels

M. V. Soldovieri[1], P. Ambrosino[1], M. De Maria[1], S. Di Sisto[1], E. Marzilli[1], L. Manocchio[1], and M. Taglialatela[1,2]

[1]*Dept. of Medicine and Health Sciences, University of Molise, Via F. De Sanctis, 86100, Campobasso, Italy*
[2]*Dept. of Neuroscience, University of Naples 'Federico II', Via Pansini 5, 80131 Naples, Italy*

Beyond their well-established role in the regulation of lipid metabolism, peroxisome proliferator-activated receptors alpha (PPARα) have been recently shown to be involved in the control of neuropathic (Kopsky et al., 2012) and inflammatory pain (Jhaveri et al., 2008; Sagar et al., 2008). Exogenous, such as fenofibrate (Oliveira et al., 2007) and GW7647 (a PPARα agonist more potent and selective than most fibrates; Russo et al., 2007), and endogenous, such as oleoylethanolamide (OEA) (Suardiaz et al., 2007), PPARα agonists exert rapid and profound anti-nociceptive effects in animal models of acute, persistent inflammatory, and neuropathic pain. These effects are reversed by co-administration of PPARα antagonists, such as GW6471 (Khasabova et al., 2012), as well as in PPARα null mice (Ruiz-Medina et al., 2012, LoVerme et al., 2006). However, the molecular pathways by which PPARα receptors activation exerts analgesic effects are poorly defined.

We have recently shown that, in F11 peripheral sensory neurons, clofibrate (0.1-1 mM) and GW-7647 (10 μM) increased $[Ca^{2+}]_i$. This effect was antagonized not only by the by PPARα antagonist GW-6471 (10 μM), but also by capsazepine (CPZ; 1 μM), a specific blocker of transient receptor potential vanilloid type 1 (TRPV1) channels, indicating that PPARα activation might facilitate TRPV1 opening (Ambrosino et al., 2013).

To further investigate this possibility, in the present study we expressed TRPV1 channels in CHO cells by transient transfection, and studied their potential activation by PPARα agonists. CLO, WY-14,643 and GW-7647 all activated TRPV1 channels; when TRPV1-expressing CHO cells were held at -60 mV, CLO, WY-14,643 and GW-7647 induced the occurrence of inward currents with $EC_{50}$s of 5.3±0.8 μM, 13.0±1.2 μM and 12.7±0.3 nM, respectively. PPARα agonist-induced currents in TRPV1 expressing cells were reversed upon co-perfusion of the TRPV1 antagonist capsazepine (3 μM), as well as by the PPARα antagonist GW6471 (10 μM). Prolonged exposure (about 30 seconds) to CLO, Wy-14,643 and GW7647 caused a time-dependent reduction (by about 84±5%, 91±6%, and 87±%3, respectively) of the current peak values evoked by each PPARα agonist, indicative of agonist-dependent TRPV1 desensitization. Preliminary data from co-immunoprecipitation experiments in CHO cells transiently expressing TRPV1 and PPARα receptors suggest a physical interaction between these two proteins, particularly in presence of the PPARα agonist GW7647 (1 μM).

Altogether, these results suggest that agonist-induced PPARα stimulation may trigger TRPV1 channels activation and desensitization. Based on these *in vitro* results, we speculate that such novel mechanism might participate in the *in vivo* analgesic effects shown by PPARα agonists.

**References**

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