THE PROGESTIN DESOGESTREL AFFECTS PHOX2B AND ITS TARGET GENES EXPRESSION: IMPLICATIONS IN THE THERAPEUTICAL APPROACHES IN CONGENITAL CENTRAL HYPOVENTILATION SYNDROME (CCHS)

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Congenital Central Hypoventilation Syndrome (CCHS, MIM 209880) is a rare neonatal disease characterized by abnormal ventilatory response to hypoxia and hypercapnia, owing to failure of autonomic respiratory control. Frameshift mutations (5%) and poly-alanine triplet expansions (95%) have been detected in the coding region of the transcription factor PHOX2B, responsible for the proper development and function of the ANS. Consistent with its role as transcriptional regulator, \transcriptional dysregulation might be an important mechanism of CCHS pathogenesis.

CCHS is a neurodevelopmental disorder, and current CCHS treatment research is aimed at counteracting the toxic effects of the mutated PHOX2B protein; in particular, drugs promoting the refolding and/or the clearance of mutant protein aggregates have proved to be effective in rescuing the nuclear localization and transactivation activity of mutants in vitro.

Very recently it has been fortuitously observed that two female patients, using the progestin Desogestrel, for contraceptive purposes, dramatically ameliorated the clinical symptoms of CCHS, showing chemosensitivity recovery (Straus et al., 2010). The molecular mechanism of this unexpected pharmacological effect is completely unknown, but this observation has strong proof of concept value, in the perspective of a pharmacological intervention in CCHS, at least for ameliorating respiratory symptoms.

Recent data in the literature reported that Desogestrel, by improving resting ventilation, increases baseline respiratory frequency of CCHS patients leading to a decrease in their PCO2 (Joubert et al., 2016). The same authors reported that in mice this increase necessitates the functioning of the serotoninergic system, thus suggesting that other neuronal systems, not depending on PHOX2B, play a key role in the amelioration of breathing defects. Furthermore, the involvement of the orexinergic system has been sustained by the findings that orexin neurons, located in the hypothalamus, are excited by relatively small changes in CO2 (Nattie and Li, 2012), providing strong evidence for their role in central chemosensitivity.

In contrast to these studies, here we show that Desogestrel affects directly PHOX2B expression and consequently the expression of some of its target genes, in a cellular context dependent manner, thus reinforcing the role that PHOX2B has in the pathogenesis of CCHS and in therapy response.

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