The Progestin Desogestrel augments PHOX2B transcriptional activity: New therapeutical approaches in Congenital Central Hypoventilation Syndrome (CCHS)

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Congenital Central Hypoventilation Syndrome (CCHS, MIM 209880), also known as Ondine's Curse, is a very rare neonatal neurocristopathy sustained by defective migration and/or differentiation of neural crest derivatives. CCHS is characterized by abnormal ventilatory response to hypoxia and hypercapnia, owing to failure of autonomic respiratory control, and affected children show an adequate ventilation while are awake but hypoventilate during sleep.
Frameshift mutations (5%) and polyalanine triplet expansions (95%) have been detected in the coding region of the paired-like homeobox gene PHOX2B in about 90% of CCHS patients. A correlation between length of the expanded tracts and both severity of the respiratory phenotype and age at onset has been reported [1,2] with the shortest poly-A expanded tract (+5 alanine residues) found in patients manifesting central hypoventilation in childhood (late onset, LO-CCHS). A more direct assessment of the role of PHOX2B in the neural control of breathing relies on the demonstration that the retrotrapezoid nucleus (RTN), a glutamatergic structure in the medulla oblongata that contains CO_2-sensitive neurons involved in the regulation of breathing, expresses PHOX2B [3], and on the generation of a novel genetically modified mouse, bearing the most frequent poly-alanine expansion (+7) observed in CCHS [4]: the heterozygous *Phox2b*$^{27/Ala+}$ offspring of the founder chimeras were born, but died in the first hours after birth from respiratory failure, with phenotypes resembling the most severe cases of CCHS and sharing the cardinal symptom of the disease, a blunted response to hypercapnia. The morphological analysis of the different neural structures expressing Phox2b and involved in breath control revealed that the retrotrapezoid nucleus did not develop in *Phox2b*$^{27/Ala+}$ mice.
As of today, CCHS appears to be a lifelong disorder, but, as no pharmacological respiratory stimulants have turned out to be effective, the ventilatory supports such as tracheotomy, nasal mask, or diaphragm pacing by phrenic nerve stimulation represent the only options available for children with CCHS [1].
Very recently it has been fortuitously observed that two females patients (20/25 and 20/26 genotype), using a progestin drug, Desogestrel, for contraceptive purposes, dramatically ameliorated the clinical symptoms of CCHS, showing chemosensitivity recovery [5]. However, the molecular mechanism of this unexpected pharmacological effect is completely unknown. In September 2011, a clinical trial has started to clarify the effect of desogestrel on ventilatory response to hypercapnia in a small cohort of female CCHS patients. On the other hand, the importance to understand the molecular mechanisms underlying the chemosensitivity recovery observed in two CCHS women after desogestrel assumption relies on the necessity to identify potential pharmacological targets for alternative molecules without contraceptive effects, to be administered chronically also to male patients.
Our initial working hypothesis was that Desogestrel enhanced the expression of *PHOX2B* or some relevant PHOX2B target genes.
Neuroblastoma cells co-transfected with PR-B cDNA, and treated with increasing amount of 3-ketodesogestrel (the active metabolite of Desogestrel) did not show any effect on the expression of endogenous *PHOX2B*, thus suggesting that the action of the progestin is not directed on increasing *PHOX2B* gene expression. Conversely, Desogestrel enhanced the expression of some relevant PHOX2B target genes in a promoter specific manner, by acting on the activity of the wild type as well as mutant protein.

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