# GESTATIONAL EXPOSURE TO RETINOIC ACID: NEUROFUNCTIONAL OUTCOMES IN MALE AND FEMALE RAT OFFSPRING

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Retinoic acid (RA) is a known human teratogen at very low doses. RA exposure during gestation results in severe malformations or more subtle abnormalities depending on the stage of brain development. The neurofunctional effects produced by developmental exposure to RA [2.5 mg/kg by gavage from gestational day (GD) 11 to 13] were investigated in the offspring of Sprague-Dawley rats. In particular, reproduction data, onset of reflexive behavior [1], locomotor activity [2], motor coordination and motor learning [3] were evaluated. The results show that RA exposure significantly increases postnatal mortality of pups ($p<0.0001$, Fisher's-exact test) and significantly decreases pup weight gain from postnatal day (PND) 12 until PND 60 with respect to the age-matched control rats (Tukey's test, male: PNDs 12, 15 and 50: $p<0.01$; PNDs 18, 21, 40 and 60: $p<0.001$; PND30: $p<0.05$; female: PND12, 40, 50 and 60: $p<0.01$; PNDs 15, 18, 21 and 30: $p<0.05$). Moreover, RA-exposed rats show a significant delay in eyes opening (male: $p<0.01$; female: $p<0.05$), hair growth ($p<0.05$) as well as in the maturation of righting reflex ($p<0.05$), cliff avoidance ($p<0.05$) and pole grasping ($p<0.05$) with respect to the age-matched control animals. Concerning motor activity assessed in the Opto-Varimex apparatus, prenatal RA treatment significantly decreases the distance travelled in male rats on PND 90 ($p<0.01$, Tukey's test) and female offspring on both PNDs 40 ($p<0.05$) and 90 ($p<0.001$), whereas the time spent in the central part of the arena in the first min of the test and the number of rearings are not altered. Finally, both male and female RA-exposed rats (PND 40) subjected to an accelerating rotation speed mode in the rotarod/accelerod task show a significant impairment in motor learning ability, while motor coordination is not impaired. In conclusion, the results show that RA exposure on GDs 11-13, at a dose near the maximum possible for survival, induces, in both male and female rat offspring, motor impairment as well as motor learning disability which are suggestive of cerebellar dysfunctions.

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