Gene absence linked to male neural development

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Research conducted by the University of Valencia (UV) and the Jaume I University of Castellón (UJI), among other institutions, has found alterations to the structure of the brain's nonapeptidergic systems, social

behavior and the production of pheromones, traits that reveal sexual dimorphism, in male mice with a lack of the Mecp2 gene. In humans, mutations of this gene cause Rett syndrome, a rare disease of the neural development which causes, among other symptoms, a loss of speech and of the ability to walk, traits of autistic diseases and epilepsy.

Nonapeptides, peptide chains with nine amino acids such as oxytocin and vasopressin, are located in the cerebral nuclei that govern social behavior, which is why they have been proposed, especially oxytocin, as possible therapies for autism disorders and related syndromes. Rett syndrome is a rare disease of the neural development caused by mutations to gene Mecp2, which mainly affects young girls, and which had traditionally been classified under the umbrella of autism disorders. To study whether the nonapeptidergic systems are impaired in Rett syndrome, which would thus justify their use as therapeutic targets, the team has analyzed them in the brain of a Mecp2-null mouse brain.

The research was co-directed by Carmen Agustín-Pavón, professor at the UV and researcher at the Mixed Unit for the Research of Functional Neuroanatomy, which includes staff from the Department of Cellular Biology, Functional Biology and Physical Anthropology of the UV and the Predepartmental Unit of Medicine of the UJI, and by Mónica Santos, from the Center of Neuroscience and Cellular Biology of the University of Coimbra, entity which has also taken part in the research, together with the University Otto-von-Guericke in Germany.

Carmen Agustín explains that "oxytocinergic and vasopressinergic substances in the brain are involved in guiding social behavior, which has sexual dimorphism in mammals, and is therefore organized differently in males and females. For example, vasopressinergic innervation is plentiful in certain cerebral nuclei, such as the septum or lateral habenula, in males, whereas in females it is practically non-existent. Our study shows that Mecp2-null males have a significant decrease in this

vasopressinergic innervation, which depends on the presence of high levels of testosterone, in all the nuclei from we call the socio-sexual brain."

In fact, as explained by Elena Martínez-Rodríguez, first signatory of the study, "as males with a mutant Mecp2 have internal testicles, our hypothesis is that the effect we see in the vasopressinergic system can take place indirectly, as a result of the deficit of testosterone, which is necessary for the dimorphic sexual development of the male brain." This hypothesis is backed by the fact that mutant females show no deficit in their vasopressinergic system. Furthermore, as an indirect measure to the level of testosterone, the team analyzed the amount of sexual pheromones in urine, and verified that male pheromone darcin disappears in mutant mice.

"Both vasopressin and testosterone are involved in regulating the social and aggressive male behavior of mice", says Ana Martín-Sánchez, currently at the Pompeu Fabra University, and first co-author of the study together with Martínez-Rodríguez. "This is why we study the response of mutant males compared to other members of the species in different situations, and we are finding that they are less aggressive than their healthy brothers, and that they prefer being near a caged member of their species to a greater extent than the healthy specimens."

Administering oxytocin

The research team did not find significant differences in the oxytocinergic system except for, in mutant males, "a slight decrease in the oxytocinergic innervation of the lateral habenula". Agustín-Pavón explains that "there do not seem to be significant deficits in the structure of the oxytocinergic system, and therefore our data does not back administering oxytocin for Rett. Furthermore, the fact that there is a heightened social preference, and not decreased, such as in the

traditional autism disorder models, is a reason for Rett to not be classified as one." The expert concludes: "our research shows how, when studying animal models with alterations to their social behavior, the possible effects of genetic mutations on the endocrine system must be taken into account, because hormone levels directly affect the structure of the social brain."

More information: Elena Martínez-Rodríguez et al. Male-specific features are reduced in Mecp2-null mice: analyzes of vasopressinergic innervation, pheromone production and social behavior, *Brain Structure and Function* (2020). DOI: 10.1007/s00429-020-02122-6

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