Editorial

Genetic modulation of oxytocin's effects in social functioning

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The contactin-associated protein-like 2 (*Cntnap2*) gene consists of 24 exons and spans 2.3 Mb at chromosome 7q35 (1). Mutations in this gene have been implicated in a broad range of neurological disorders such as autism spectrum disorders (ASD), schizophrenia, intellectual disability, dyslexia, language impairment, cortical dysplasia and focal epilepsy (2,3). Intriguingly, individuals carrying mutations in the *Cntnap2* gene seem to show similar abnormal phenotypes such as intellectual disability, seizures, language and social abnormalities (2).

Social abnormalities as well as communication and language deficits are characteristic core behavioural features of ASD, a group of neurodevelopmental disorders (4). Although the pathogenesis of ASD is not yet well known, there is strong evidence from twin studies that genetics play a crucial part (5-7). While earlier studies implicated the influence of genetic components in the range of about 90%, more recent findings lowered this estimate (to about 50%), emphasizing instead interaction with contributory environmental factors (8,9). For example, environmental factors such as smoking, alcohol, medication and pesticides have been consistently implicated (8). To date, early genome-wide linkage studies and more recently, genome-wide association studies (GWAS) in huge samples sizes have been able to highlight several vulnerability genes. However, replications are unfortunately still infrequent and inconsistent (10-14). Thus, we embrace the hypothesis that genetics might account for only a part of the aetiology of ASD. However, genetics remains a key influential factor that might constitute a basis for differential developmental trajectories as well as for different reactions to environmental elements, including therapeutic treatments.

The neuropeptide oxytocin (OXT) has been shown to be an important modulator of social behaviours such as social recognition, social memory, pair bonding, sexual behaviour, paternal and maternal care (15-20). Conceivably, this has led to considerable interest in the oxytocinergic system as a potential therapeutic target in the treatment of social behavioural impairments in neuropsychiatric disorders such as ASD (21,22). Despite early promising findings (14,23-26), thus far, preclinical experiments in animal models and preliminary clinical studies in humans have produced conflicting results of oxytocin's pro-social effects (27,28). Some trials have shown moderate improvement in social function in adults and children, but others have not yielded any positive effects (27,29). Notably, various pieces of research suggest that chronic exogenous OXT treatment in subjects with relatively normal functioning oxytocinergic systems might actually cause detrimental effects (28,30). Altogether, these findings highlight the importance of dealing cautiously with therapeutic use of OXT, and that more research is still needed in this promising field. In this context, genetically modified mouse models might prove to be invaluable tools in our future investigations and help to implement/improve the use of OXT as a therapeutic tool.

In line with this, the recent work by Peñagarikano and coworkers in issue 271 of *STM* 2015 (31) constitute one of the first important examples. In particular, these authors have previously characterized a mouse model of autism where the *Cntnap2* gene, responsible for cortical dysplasia and focal epilepsy syndrome, is knocked out. These mice have been shown to display social deficits. Now, in their recent report, the authors observed that an acute (both intraperitoneal and intranasal) dose of OXT or arginine vasopressin (AVP) was able to rescue the social behavioural deficits observed in Cntnap null mutant mice (–/–). Further experiments suggest that these behavioural improvements might be more dependent on OXT pathways as the OXT

receptor antagonist L371,257 was also able to block the prosocial effects of AVP in Cntnap$^{-/-}$ mice. Furthermore, additional behavioural tests revealed that the effects of OXT were specific to social behaviour, in agreement to what has already been shown following exogenous OXT in wild-type mice (28,30). Unfortunately, in Peñagarikano's work, mice carrying a partial genetic disruption of the Cntnap2 (i.e., heterozygote +/–) or knock-in with a human-like mutation have not been investigated. This will be crucial in a translational perspective, as it might better mimic the genetic variations that could be present in human subjects.

An interesting point reported in Peñagarikano's work support increasing evidence indicating that different receptors expressed on OXT neurons could be targeted using pharmacological agents to stimulate OXT release. Ultimately, these non-OXT drugs that enhance endogenous oxytocin release, could be the most effective in stimulating the oxytocinergic system in a more physiological way in order to improve social abnormalities. In agreement, acute melanocortin-4 receptor (MC4R) agonist treatment, which activate PVN OXT neurons (32) and induce central OXT release (33), remarkably improved Cntnap2$^{-/-}$ social deficits. Moreover, this effect was absent in wild-type mice and it was blocked in Cntnap2$^{-/-}$ when an OXT receptor antagonist was previously administered.

The next question would be, how to reconcile these clearly positive effects of OXT in social behaviour with the mixed results obtained so far in the clinic and in wild-type mice? The key is the status of the endogenous OXT system! Indeed, in Cntnap2$^{-/-}$ mice, the number of OXT-expressing cells in the PVN is reduced in comparison with wild-type littermates. Correspondingly, reduced OXT levels were also found in radioimmunoassay analysis of whole brain extracts. These findings support still preliminary evidence that only subjects with abnormal brain OXT systems might be expected to manifest ameliorative effects following OXT treatment. It will be important to demonstrate this in order to build a foundation for more effective and personalized healthcare in ASD.

Finally, the authors commenced investigating the effects of early postnatal sub-chronic intranasal administration of OXT in Cntnap2$^{-/-}$ and wild-type mice. Interestingly, in contrast to chronic treatment in adult mice (28), exogenous OXT during development seemed to be completely ineffective in wild-type mice. This might suggest that maybe during early development of the OXT system, exogenous OXT might not be deleterious. However, to strengthen this conclusion, quantification of endogenous OXT levels should have been performed not only in Cntnap2$^{-/-}$ mice, but also in wild-type mice following the early postnatal treatment. Despite this, these novel findings put forth an important conjecture that OXT treatment in early critical developmental windows, and particularly in OXT-deficient systems, could bring about diverse outputs and longer lasting effects on social behaviours compared to treatment during adulthood.

In conclusion, the work by Peñagarikano and co-workers has added valuable knowledge about the potential benefits of OXT manipulation in ameliorating social deficits and its interaction with the genetics of ASD. Even though at the moment, it is still unclear whether a compromised oxytocin system contributes to the aetiology of ASD (14,34-36), further knowledge about gene variations that might impact the OXT system in different ways will prove to be valuable in order to identify which subjects might most likely benefit from treatments targeting the OXT system. Further parallel studies in animals and humans are required to address these issues and to investigate the interaction of genetics with potential oxytocin treatments.

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