Could a treatment for Parkinson's disease help the social impairment of diseases like autism?

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A stressful pregnancy might be the last thing a future mother needs, but it is to her unborn baby that this stress spells real trouble. All because stress hormones (called glucocorticoids or GCs) can change foetal brain development, causing the new individuals to develop serious behavioural and/or emotional problems. Despite this danger we remain far from understanding how GCs work. But now a study in rats by a Portuguese team has discovered that the prenatal (before birth) effect of GCs on behaviour is linked to problems in dopamine (a brain messenger). Surprisingly, they also found that it is possible (and easy) to reverse the abnormal behaviours seen in these individuals, a discovery with possible implications for neurological diseases like autism and attention-deficit hyperactivity disorder (ADHD).

Sonia Borges and Barbara Coimbra from the University of Minho found that when rats are exposed to high levels of GCs during its foetal formation, not only they develop abnormal behaviour, but their dopamine levels are lower than normal in several brain areas linked to pleasure. Once normal levels are restored, though, the emotional and social abnormalities seen in these animals disappear. This seems to show that brain changes triggered by early life trauma could be reversed by dopamine, what is remarkable. The study, which is coming out September in the journal *Neuropsychopharmacology*, has implications for neuropsychiatric disorders associated with dopamine and early neurodevelopmental problems, such as depression, anxiety, ADHD,

schizophrenia and autism. Ana João Rodrigues, one of study leaders (together with Nuno Sousa) warns for the need to be very cautious though " Although there are some clues that prenatal stress may affect emotional and social behaviour in humans, our work is still at very early stages. All we can really say" – she points – "is that dopamine is able to improve deficiencies in social behaviour and this might have important implications for diseases characterised by social impairment".

GCs are crucial life hormones – if they mediate the negative effects of stress, they are also involved in all types of normal functions of the body; from controlling the immune system and regulate the metabolism to even help the maturation of foetal organs, GCs are indispensable for life. In fact, even if they can provoke problems in the foetal brain, these hormones are still routinely given to pregnant women in danger of premature delivery, to help foetal lung maturation. So it is urgent to understand better how GCs work to be able to make better crucial, even life-depending, decisions.

So in the study to be published Borges, Coimbra and colleagues looked at their effects before birth, by exposing rats still in the uterus to high levels of GCs (the equivalent of having a very stressed mother), and found that they went to develop signs of depression and lack of motivation (like reported before), but they also saw social impairments. Animals exposed to prenatal stress played less, had less "happy" calls ("happy" and "sad" calls can be differentiated by their sound frequencies) but also interacted awkwardly with others.

"Since our group had seen before that exposure to prenatal GCs affected a neural circuit important for the feelings of reward and pleasure (the mesolimbic system) " - explains Rodrigues - "and in juvenile rats rough tumble and play is one of the most rewarding behaviours, we wondered if the problem could be dopamine, a key molecule in this system."

And in fact, it was found that "prenatal stress" rats lacked dopamine in both the amygdala and the nucleus accumbens (NAc), which are regions of the mesolimbic system. But what was remarkable was the next discovery – that L-dopa (a precursor of dopamine given to Parkinson's patients who also lack it) simply added to the water of the affected animals was enough to fully reverse their social and emotional abnormalities.

So the new study reveals that high GC levels/prenatal stress can lead to social impairments, as well as the emotional problems seen in previous studies, and this appears to result from reduced dopamine levels in brain areas linked to pleasure perception. And once these animals' dopamine levels are corrected the behavioural problems are also corrected.

So could things work similarly in humans? In diseases like depression, autism and schizophrenia, which are characterised by emotional and social inadequacies and/or have already been linked to prenatal stress? Rodrigues alerts "To transfer these results to humans requires caution. These results do not mean that L-dopa is a miraculous drug to treat lack of motivation or depression, although it certainly appears that the mesolimbic dopamine system is critical in these problems. For now the most important thing is that we are starting to unveil GCs' induced molecular changes in specific neuronal circuits, which will help in the understanding of some of these problems".

Borges and Coimbra's study is interesting also because it finally "links the dots" – prenatal stress has already been associated to an increased incidence of several neurologic diseases and some of these to problems in dopamine. Social impairments like those seen autism and ADTH on the other hand are known to be more common in individuals that went through stressful prenatal periods. What the new study manages to reveal now is the "underneath story". And, of course, introduce the possibility of a treatment.

But the work had one other interesting result: when the social behaviour of the animals was being tested two rats exposed to prenatal stress put together didn't play but, surprisingly, the interaction of one of these and a normal animal had very different results. This because the normal individual would not rest inciting and provoking the "disturbed" rat to play until it finally started interacting. This supports the idea that interaction with other individuals can make a vital difference to revert the negative effects of pre-natal or early life stress on the brain, and should be encouraged as early as possible.

More information: Dopaminergic modulation of affective and social deficits induced by prenatal glucocorticoid exposure, *Neuropsychopharmacology* (September 2013) 38, 2068–2079; doi: 10.1038/ npp.2013.108

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