

How does Prozac act? By acting on the microRNA

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The response time to [antidepressants](#), such as [Prozac](#), is around three weeks. How can we explain this? The adaptation mechanisms of the [neurons](#) to antidepressants has, until now, remained enigmatic. Research, published this week by the teams of Odile Kellermann (Inserm Unit 747 Cellules souches, Signalisation et Prions, Université Paris-Descartes) and of Jean-Marie Launay (Inserm Unit 942 Hôpital Lariboisière, Paris and the mental health network, Santé Mentale), sheds new light on the mechanisms of action of these drugs which have been used for more than 30 years and are heavily consumed over the world. In particular, the researchers have revealed, for the first time, a sequence of reactions caused by Prozac at the neuron level, which contributes to an increase in the amounts of serotonin, a chemical "messenger" essential to the brain, and deficient in depressive individuals.

Details of this work are published in the journal *Science* dated 17 September 2010.

Depressive states are associated with a deficit of serotonin (5-HT), one of the neurotransmitters essential for communication between neurons and particularly involved in eating and sexual behaviours, the sleep-wake

cycle, pain, anxiety and mood problems.

Strategies employing antidepressant class I molecules, developed since the 1960s are thus primarily aimed at increasing the quantity of serotonin released in the synaptic gap, the space between two neurons, where the nervous communications take place via the neurotransmitters. Although it has been known for several years that antidepressants like Prozac have the effect of increasing the concentration of serotonin by blocking its recapture by the [serotonin transporter](#) (SERT) in the synapses, we did not hitherto know how to explain the delay in their action (3 weeks).

The teams of Odile Kellermann and of Jean-Marie Launay, in close collaboration with Hoffmann-LaRoche (Basel), have now characterised, for the first time, in vitro and then in vivo, the various reactions and intermediate molecules produced in the presence of Prozac, which are eventually responsible for an increased release of serotonin. In particular, the researchers have identified the key role of one particular microRNA in the active mechanisms of the antidepressants on the brain*.

This microRNA, known as miR-16, controls synthesis of the serotonin transporter.

Under normal physiological conditions, this transporter is present in the so-called "serotonergic" neurons, i.e. neurons specialised in production of this neurotransmitter. However, expression of this transporter is reduced to zero by miR-16 in so-called "noradrenaline" neurons, another neurotransmitter involved in attention, emotions, sleep, dreaming and learning.

In response to Prozac, the serotonergic neurons release a signal molecule, which causes the quantity of miR-16 to drop, which unlocks

expression of the serotonin transporter in the noradrenaline neurons.

These neurons become sensitive to Prozac. They continue to produce noradrenaline, but they become mixed: they also synthesise serotonin. Ultimately, the quantity of released serotonin is increased both in the serotonergic neurons, via the direct effect of the Prozac which prevents its recapture, and in the noradrenaline neurons through the reduction of miR-16.

Hence, "this will work has revealed, for the first time, that antidepressants are able to activate a new 'source' of serotonin in the brain", explain the researchers "Furthermore, our results demonstrate that the effectiveness of Prozac rests on the 'plastic' properties of the noradrenaline neurons, i.e. their capacity to acquire the functions of serotonergic neurons".

To elucidate the mode of action of Prozac, the researchers from the Ile-de-France region used neuron stem cells which were able to differentiate themselves into neurons for manufacturing serotonin or noradrenaline. The cells, isolated and characterised by the two research teams, allowed them to reveal using pharmacological and molecular approaches, the functional links between Prozac, miR-16, [serotonin](#) transporter and the signal-molecule trigger, known as S100Beta. These links observed in vitro have been validated in vivo in mice, in the serotonergic neurons of the raphe and the noradrenaline neurons in the locus coeruleus. Dialogue between these two areas of the brain, situated under the cortex in the brainstem, is therefore one of the keys to Prozac action.

Behavioural tests have moreover confirmed the importance of miR-16 as an intermediary in Prozac action.

These results open up new avenues of research for the treatment of depressive states. Each of the "actors" in the sequence of reactions

initiated by Prozac constitutes a potential pharmacological target.

The pharmacological dynamics of antidepressants, i.e. the study of the speed of action of these molecules, should also be the subject of new investigations in light of these new ideas.

More information: "miR-16 Targets the Serotonin Transporter: A New Facet for Adaptive Responses to Antidepressants" *Science*, September 17th 2010, vol. 329, 5998.

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