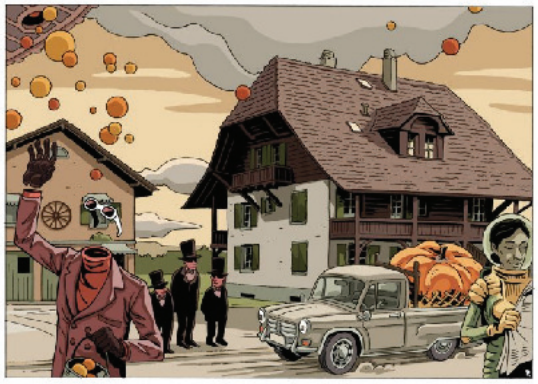
# a balanced mind

Vivienne Baillie Gerritsen

**When I leave for work every morning, I know exactly where to get my train. This may sound quite absurd but just imagine, for one moment, that you had no memory. You would always be losing your keys. You would never remember where you had left your shoes. And you'd probably fall down the front doorstep daily because you had forgotten there was one. Thanks to our faculty for memorising things, life is far easier for us. We learn how to talk. We learn to avoid awkward situations. We even remember who our children are. On the molecular front, there is a lot going on. It all has to do with neurons and their ability to pass on messages and connect to one another. Unsurprisingly, many proteins are involved in the processes of learning and memory, and much research has been done on them in the past years. There is one protein, however, known as RGS14, which is a bit of a conundrum. Indeed, RGS14 seems to have the intriguing role of suppressing memory...**



by PET

Courtesy of the artist

Deliberately suppressing the ability to remember something may sound unreasonable. Yet the art of forgetting is also important. We have to forget all the words we hear throughout the day. We have to forget all the prices we see on a restaurant's menu. We have to forget all the faces we brush past as we rush across town. Our brain needs to filter the hundreds of thousands of messages we bump into every day. If it doesn't, we would all be on the verge of madness. Memory is thus a question of balance between remembering some things and forgetting many others.

The notion is not new. There is a psychiatric disorder known as the Savant Syndrome* caused by the malfunction of a phosphatase, PP1, which – in natural circumstances – hinders the synthesis of proteins involved in memory. Those inflicted with the disorder are submerged with useless information they are unable to forget. Hence, the importance of a basic memory filter. So why all the fuss about RGS14? Because RGS14 not only belongs to a part of the brain which, until now, had shown no involvement whatsoever in the memory process but also because when it is shut off, memory seems to be enhanced without any side effects. Which sounds like magic...

Current wisdom suggests that, in the brain, the seat of memory and learning is situated in the hippocampus. Until recently, one small region known as CA2 had been neglected by researchers because – unlike the rest of the hippocampus – it didn't seem to have any say in memory. But it turns out that it does, in a certain sense. Indeed, CA2 is full of RGS14. So, yes, in natural circumstances, RGS14 suppresses the faculty of memorising. But when the protein was silenced in mice, scientists discovered that the rodents were not only intrigued by new objects – thus meaning that they had recognised pre-existing ones which were consequently of less interest – but they were also far brighter than their wild-type companions at making their way through a maze.

So what is happening on the molecular level? The answer is synaptic plasticity. Memory is believed to be a case of synaptic transmission between neurons, and the strengthening of such

connections. This has been termed synaptic plasticity and forms the basis of acquiring and consolidating certain forms of learning and memory. These processes are known to occur in the hippocampus, save in the CA2 region. Which is one of the reasons this region had been ignored until now. So, if synaptic plasticity is at the heart of memory, how does RGS14 act upon it?

RGS14 belongs to the very large family of G protein signalling regulators (RGS) and directly suppresses the activity of a certain number of proteins whose downstream effects would otherwise be crucial in the processes of learning and memory. More specifically, RGS14 binds to G proteins as well as to components of the mitogen-activated protein (MAP) kinase signalling pathway – both of which are required to strengthen synaptic transmission. When the effects of RGS14 are wiped out in mice for example, G protein and MAP kinase signalling pathways are free to be activated, synaptic plasticity is restored and the rodents' capacity to remember objects is enhanced. Thus making them somewhat smarter than they otherwise were expected to be.

What is more, putting a rein on RGS14 doesn't seem to have any side effects on the mice's psyche. For as much as one can really measure such a subtle state of things. But, once again, a mouse is not human, and there is a great chance that RGS14 is part of our brain – or a rodent's – for a reason other than memory. To be sure, the rest of the hippocampus does that… Perhaps RGS14's faculty of suppressing memory is just a side effect of something far more important it can do that we are unaware of. After all, the loss of neurons in the CA2 region is known to be involved in psychiatric disorders such as schizophrenia for instance. This said, RGS14 is restricted to CA2, itself a discrete region of the hippocampus, which makes the protein an ideal candidate for the future design of therapeutic agents that could ease psychiatric disorders. Or simply help to diminish the increasing ease with which we forget things over the years.

***N.B. Also read Protein Spotlight issue 32, "The things we forget"***

## Cross-references to UniProt

Regulator of G protein signaling 14 (RGS14), *Mus musculus* (Mouse) : P97492
Regulator of G protein signaling 14 (RGS14), *Homo sapiens* (Human) : O43566

## References

1. Vellano C.P., Emerson Lee S., Dudek S.M., Hepler J.R.
RGS14 at the interface of hippocampal signaling and synaptic plasticity
Trends in Pharmacological Sciences [Epub ahead of print] (2011)
PMID: 21906825

2. Emerson Lee S., Simons S.B., Heldt S.A., Zhao M., Schroeder J.P., Vellano C.P., Cowan D.P., Ramineni S., Yates C.K., Feng Y., Smith Y., Sweatt J.D., Weinshenker D., Ressler K.J., Dudek S.M., Hepler J.R.
RGS14 is a natural suppressor of both synaptic plasticity in CA2 neurons and hippocampal-based learning and memory
PNAS 107:16994-16998(2010)
PMID: 20837545

3. Shu F.-j., Ramineni S., Hepler J.R.
RGS14 is a multifunctional scaffold that integrates G protein and Ras/Raf MAPkinase signalling pathways
Cellular signaling 22:366-376(2010)
PMID: 19878719