In an effort to understand the mechanisms that stress initiates, Dr Jean-Michel Revest has developed a thorough understanding of a molecular pathway through which stress affects memory and encourages the progression of psychiatric disorders.

Can you provide a context for your research and describe your main objectives?

My research is based on the understanding of the physiological mechanisms initiated by stress. These mechanisms are necessary for an organism to adapt to a sudden change of environment, such as a threat, and produce a response proportional to the stimuli. However, the future survival of the organism will be largely conditioned by its ability to store information about the stressor to further produce an appropriate and efficient response if the event reoccurs. Conversely, excessive chronic stress may lead to cognitive impairments such as hypermnnesia and amnesia, which contribute to the development of psychiatric disorders including depression, anxiety and post-traumatic stress disorder (PTSD).

My main objective is to understand the cellular and molecular mechanisms through which stressful events induce a higher memory trace than those with a low affective valence. This is central to the pathophysiology of many psychiatric diseases in which people are unable to forget certain events. In this context, I have focused on the molecular signalling pathway mediating the memory enhancing effects of glucocorticoid hormones (GC).

What are GC and how do they interact with glucocorticoid receptors (GR)? Could you discuss their roles in memory?

GC are commonly called stress hormones because they are produced and released by the adrenal glands during the active phase of the circadian cycle and in response to stress. GC are involved in many physiological processes in the central nervous system (CNS).

In the CNS, GC activate two nuclear receptors: the ubiquitously neural-expressed GR and the mineralocorticoid receptor, present in discrete brain regions. Both receptors are hormone-activated transcription factors that bind to GC and translocate to the nucleus where they change the expression of target genes. The GR have a low affinity for corticosterone and are only activated when the levels of the hormones are high, as is the case during stressful experiences. In particular, the GR are expressed in specific brain regions: the hippocampus, amygdala and prefrontal cortex. These structures play an important role in memory processes, including encoding and retrieval of information of emotional events.

Consequently, identifying the cellular and molecular targets of GC-activated GR appears to be crucial to understanding the molecular mechanisms by which environmental changes influence the activity of the CNS and induce behavioural impairments.

Your research initially focused on the Erk1/2MAPK signalling pathway as mediating the memory enhancing effects of GC. What did you discover?

The Extracellular signal-Regulated Kinases 1/2 Mitogen-Activated Protein Kinases (Erk1/2MAPK) signalling pathway constitutes a widely conserved family of intracellular serine and threonine protein kinases. We initially investigated whether the Erk1/2MAPK signalling pathway could be a molecular target of GC-activated GR for several reasons. First, Erk1/2MAPK is often activated concomitantly with the GR; for example, after stress, during learning tasks or in response to drugs of abuse. Furthermore, this signalling pathway plays an important role in regulating consolidation of memory.

Briefly, our studies emphasised that the activation of the Erk1/2MAPK pathway (occurring within the hippocampus, and in particular of Erk1/2MAPK phosphorylation) is crucial in mediating the behavioural effects of GC, allowing the enhancement of contextual fear memory.

Recently, you examined how brain-derived neurotrophic factor (BDNF) acts to mediate the fear memory enhancement induced by GC by signalling through Erk1/2MAPK phosphorylation. Why did you target BDNF?

We chose BDNF as a target for several reasons. First, both hippocampal BDNF mRNA production and GR activation are observed after acute stress and during contextual fear conditioning. These behavioural procedures greatly depend on GC.

Second, BDNF is a major molecular player in the regulation of memory processes and related physiological functions, such as synapse formations and synaptic plasticity. For example, invalidation of the BDNF gene motivated memory losses in a context-dependent fear-conditioning procedure.

Third, the cellular effects of BDNF, mediated by the activation of the Tropomyosin-related kinase B (TrkB) receptor, involve the activation of the Erk1/2MAPK pathway in many cases. In line with this observation, TrkB knockout mice, and transgenic mice overexpressing TrkB experienced reduced and enhanced hippocampal-dependent memory, respectively.

Are there applications in relation to stress-related behavioural responses that you anticipate arising from your work?

Our recent findings complete our knowledge of the molecular cascade through which GC enhance contextual fear memory and highlight the role of tPA-BDNF-TrkB-Erk1/2MAPK signalling pathway as one of the core effectors of stress-related effects of GC. The understanding of this key molecular pathway is crucial to identifying new molecular targets that will make it possible to design selective innovative therapies for stress-related disorders such as depression, anxiety, PTSD.
One of the ways our bodies respond to stressful stimuli is to affect our ability to develop and retain memories. Scientists say this memory effect has probably evolved as a way for organisms to cope with the stress caused by a sudden change of environment in some threatening way. For example, if an animal survives a dangerous situation such as a close encounter with a predator, an increased memory of the event will enable the animal to avoid a similar hazard in the future, improving its likelihood to survive and pass on this biological response to its offspring. However, in the case of the human brain, this evolutionary adaptation in some situations has switched from being a useful survival tool to being a major impairment or contributing factor in depression, anxiety and post-traumatic stress disorder (PTSD).

**Stress Hormones**

Dr Jean-Michel Revest’s work at the French Institute of Health and Medical Research (INSERM) has begun to build the foundations of knowledge underlying the specific physiological mechanisms that stress initiates. His work on the memory enhancing effects of glucocorticoid hormones (GC) has illuminated a direct pathway between increased stress levels and improved memory in the short term.

GC are a class of steroid hormones produced by the adrenal glands. Generally, they are released following the circadian rhythm when a person is awake, and their production skyrockets in response to stressful stimuli. The GC produced due to a stressful stimulus binds to glucocorticoid receptors (GR), which are hormone-activated transcription factors that affect the transcription of target genes to mRNA and ultimately proteins. In the absence of GC, GR are associated to heat shock proteins (HSP) in the cytoplasm of the cell. This association holds GR in a conformation that makes it incapable of binding to DNA and acting as a transcription factor. However, after binding to GC, the GC-activated GR dissociate from the HSP and can then move from the cytoplasm to the nucleus of the cell. Here, the complex can modify the expression of genes by binding to specific palindromic DNA sequences located in the cis-regulatory region of target genes.

**Molecular Pathway**

Revest and colleagues analysed DNA sequences of many genes deemed likely to be involved with the presence of glucocorticoid responsive elements. They focused on genes producing behaviours similar to those exerted by GC and whose expression was sensitive to the effects of stress. This search highlighted several genes, which pushed the researchers to selectively focus on two corresponding proteins: pro-brain-derived neurotrophic factor (pro-BDNF) and tissue plasminogen activator (tPA). Through focusing on these two proteins, Revest and his team have been able to create a description of the tPA-BDNF-TrkB-Erk1/2MAPK signalling pathway and its role in the enhancement of memory.

Molecular signalling pathways are vital throughout the body, particularly in the brain, as they provide a way for cells to communicate with each other. Their communication can be imagined as a relay race in which the runners are the molecules or proteins and the baton is a message. Each part of the pathway passes this message on to the next until it reaches the finish line, where the message causes an effect such as an increase or decrease certain bodily functions.

The pathway specific to Revest’s research starts with the GC-induced expression of pro-BDNF and tPA proteins. The tPA, the role of which is to cleave plasminogen to plasmin, allows the proteolytic processing of the pro-BDNF protein into mature BDNF. Once mature, the BDNF can then bind to the Tropomyosin-related kinase B (TrkB) receptor. Consequently, the TrkB is phosphorylated; phosphorylation of proteins is a common step in molecular signaling pathways and is equivalent to the handing of the relay baton in a race. The phosphorylation of the TrkB in turn leads to the phosphorylation of the extracellular signal-regulated kinases 1/2 mitogen-activated protein kinases (Erk1/2MAPK) and of the activation of downstream transcription factor, Egr-1.

These final proteins in the sequence can then go on to modify protein expression and phosphorylation...
Specific Enolase (NSE) marker in the dentate gyrus of the hippocampus of genetically-modified mice, merges of the two signals are shown.

These phenotypes are associated with specific modifications of target genes suggesting that GR-dependent behavioural modifications induce expression of a specific set of target genes*.

PATH TO SUCCESS

Treatments for both depression and PTSD are likely to benefit from this work, as both are associated with a deregulation of GC and BDNF. With PTSD, which is characterised by the paradoxical association of amnesia for peri-traumatic contextual cues and hypermnesia for simple salient trauma-associated stimuli, this increased memory effect could be the main factor causing the disorder, as the sufferer cannot forget the stressful event, preventing recovery. Additionally, stress does not always lead to increased memory, as is shown in cases where excessive chronic stress has caused cognitive impairments, such as amnesia. These data could suggest that the shift from a facilitating effect on memory of a short lasting stress to a deleterious one induced by prolonged stress could be mediated by a fine switch mechanism enhancing or decreasing BDNF levels, respectively.

As a consequence, there are a number of unsolved issues Revest intends to tackle. For example, he wants to study the molecular mechanisms underlying the BDNF proteolytic processing. An oscillation in the balance between pro-BDNF and BDNF levels could have profound physiological implications and the mechanism for control of this ratio represents one of many therapeutic targets.

Memory is a poorly understood yet hugely important area of neuroscience and psychology. The level of mystery would be a clear incentive for scientists regardless, but the potential to improve the lives of so many with neurological conditions gives this work clear impetus. As Revest states: “The understanding of this key molecular pathway is crucial to identifying new molecular targets that will make it possible to design selective innovative therapies for stress-related disorders.”

INTELLIGENCE

MOLECULAR BASIS OF STRESS-RELATED DISORDERS INDUCED BY STEROID HORMONES

OBJECTIVES

To identify the cellular and molecular targets within the central nervous system at the base of the pathophysiology of behaviours, especially those involved in behavioural disorders associated with stress (ie. traumatic memory, anxiety, depression and post-traumatic stress disorder) and the addiction to drugs of abuse (ie. cocaine and tetrahydrocannabinol). The project includes a specific focus on the study of the molecular signalling pathway mediating the memory enhancing effects of glucocorticoid hormones.

KEY COLLABORATORS

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JEAN-MICHEL REVEST started his graduate studies in the University of Marseille where he received a PhD in Cellular Biology, Structural Biology and Microbiology in 1998 under the supervision of Dr Geneviève Rougon. He then moved to London to work as a postdoctoral fellow with Dr Clive Dickson at the Imperial Cancer Research Fund where he studied the role of receptor tyrosine kinases in breast cancer development and learnt the basis of the gene transfer technology. In 2001, recruited as a CNRS tenured researcher, he joined the group of Dr Pier Vincenzo Piazza at the Neurocentre Magendie to develop molecular and transgenic projects to study the cellular and molecular basis of stress-related behavioural disorders.

CONFOCAL DISTRIBUTION OF EGFP PROTEIN – MIMICKING ΔGR PROTEIN – AND ENDOGENOUS NEURON SPECIFIC ENOLASE (NSE) MARKER IN THE DENTATE GYRUS OF THE HIPPOCAMPUS OF GENETICALLY-MODIFIED MICE.