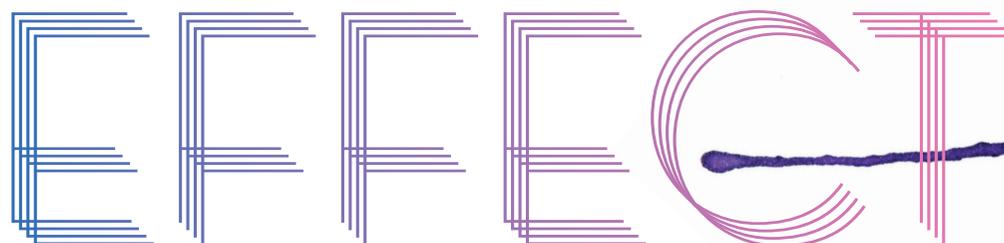


# UNEXPECTED



Corticoids activate  
inflammation mechanisms  
in certain areas of the brain

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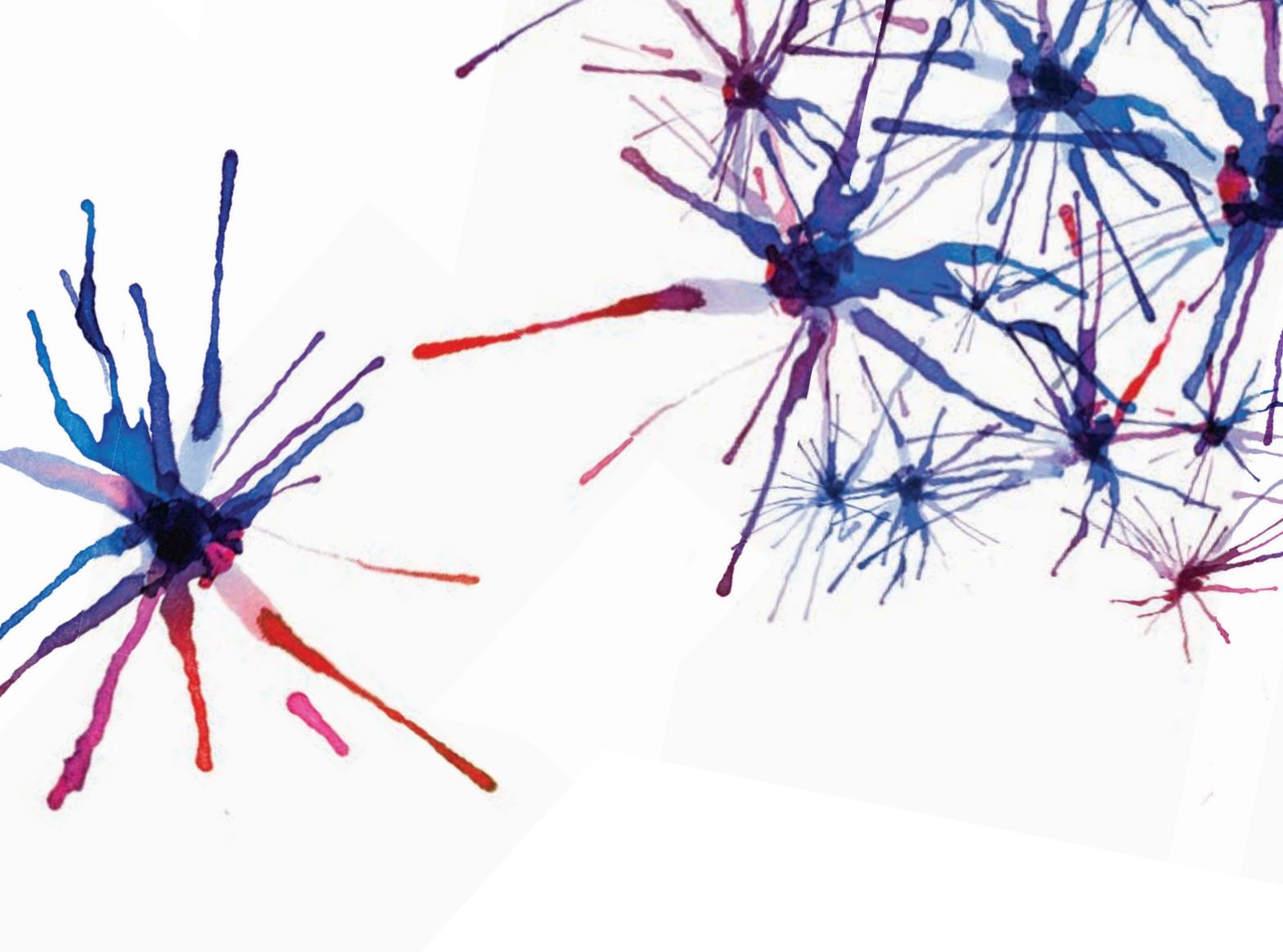
**T**he one percent of the world's population living with the terrible pain of rheumatoid arthritis, a chronic inflammation that causes articulations to degenerate, is well aware of the importance of corticoids in improving the quality of life. Over the last few decades, the millions who suffer from respiratory allergies, skin diseases, brain tumors and a variety of other conditions in which the body's inflammation response is exaggerated have also benefited from the powerful anti-inflammatory effects of these compounds, which are generally synthetic derivatives of cortisone, the main corticoid secreted by the human adrenal glands.

Identified by Edward Calvin Kendall and Philip Showalter Hench at the beginning of the last century (the discovery earned them the Nobel Prize for Medicine in 1950), corticoids do not, however, always work as expected, particularly in the case of synthetic hormones. In some areas of the brain, the effect may be the exact opposite of what is expected, causing increased inflammation, as was suggested by Carolina Demarchi Munhoz and Cristoforo Scavone of the University of São Paulo (USP) and Robert Sapolsky of Stanford

University in their study published in the *Journal of Neuroscience* in late 2010.

By means of an intravenous injection of bacteria fragments, this group of researchers induced inflammatory responses in laboratory rats to assess the power of corticoids to modulate biochemical reactions caused by brain inflammations, such as those that occur in the case of tumors or strokes. It is known that the body's natural response to inflammation is the secretion of corticoids – and the adrenal glands of rats produce corticosterone, a hormone similar to human cortisone.

Before provoking inflammation, Munhoz removed the rats' adrenal glands (adrenalectomy) and implanted slow-release corticosterone capsules under their skin. Thus, by controlling the dosages, she was able to investigate whether the anti-inflammatory action varied depending on the different levels of corticoids in the blood of the animals. The rats were separated into three groups, each with a different hormone dose. The first group received a low level of corticosterone, equal to that normally produced by the rodents; the second group received a medium dose, similar to what is found in the body in cases of light stress,



such as the sudden fright caused by an unexpected slamming of a door; and the third group received a high dose, which corresponded to moderate levels of stress, such as worry over the inability to pay one's bills. The control group was composed of rats whose adrenal glands had not been removed.

The relation between levels of corticoids in the blood and levels of stress is important because this adaptive reaction by the body to new or threatening situations also causes the adrenal glands to release corticoids. Years before, this group of researchers had already shown that chronic and unforeseeable stress may cause brain inflammation (see *Pesquisa FAPESP issue 129*), but their more recent research investigated if and how corticoids mediate this effect.

Using immunology and molecular biology techniques, this study evaluated how each level of corticoids affected two distinct regions of the rats' brains: the hippocampus (involved with memory, learning and, in pathological situations, the development of epilepsy) and the frontal cortex (associated with more advanced cognitive processes, such as decision-making). They observed a complex pattern of response in the analyzed genes.

Depending on the dose, some genes functioned with the same pattern in the two regions (i.e., being activated or deactivated in both); however, others worked differently (i.e., being active in one and inactive in the other). These changes resulted from control over the activity of the nuclear factor kappaB (NF-kappaB), an intracellular communication molecule that is key to the biochemical process that regulates the inflammation response.

Previously, it had been believed that NF-kappaB was always blocked by corticoids, which would then have an anti-inflammatory effect. Indeed, in the highest dose, the corticoids reduced NF-kappaB activity and inflammation of the hippocampus. However, at the low and medium levels, they enhanced the effect of NF-kappaB, thereby enhancing the signal that triggers inflammation. The relation was different in the frontal cortex; there, the high dose of corticosterone was anti-inflammatory, whereas the intermediary dose made the inflammation more severe.

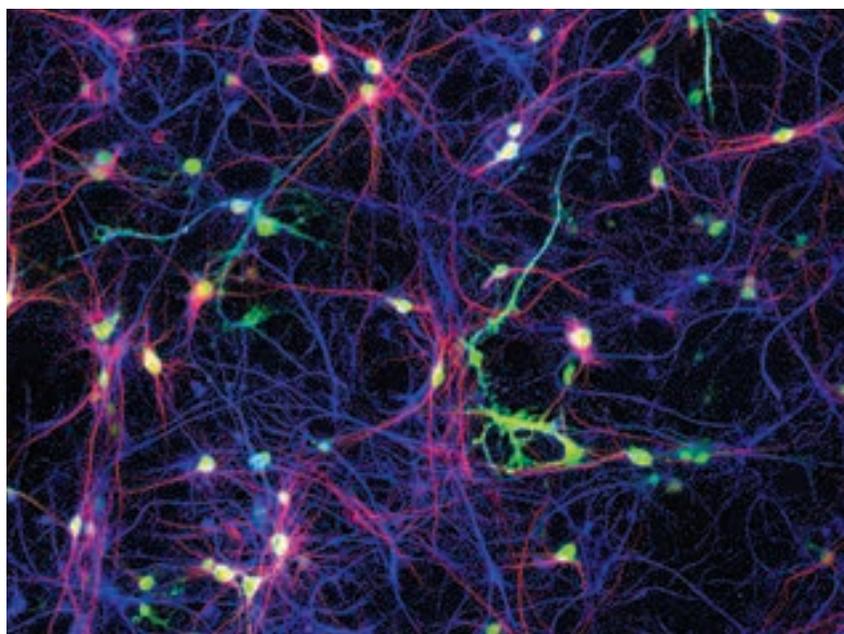
Although these results are experimental, they may prove to be of clinical importance, particularly for neurology and psychiatry, both of which deal with brain inflammation and its consequences.

According to Munhoz, the doses used in the tests with rats are close to those administered in human studies. However, she proposes that the data be examined cautiously: “We showed that the effect of corticoids, even at appropriate doses, isn’t just anti-inflammatory; however, the work was done with rats, using their natural corticoid.”

The fact that the researchers used a natural corticoid in the experiments can make a considerable difference. The corticoids produced by the body work differently than synthetic corticoids used as medication. One difference is that only 10% of the corticoids secreted by the adrenal glands are in free form in the blood, ready to act on both peripheral tissues and the central nervous system. Synthetic corticoids, however, are readily able to act on peripheral tissues, but they are, to a significant extent, filtered when they enter the brain’s circulation, as a special barrier (hematoencephalic) lines the brain’s blood vessels and controls the passage of various compounds.

Therefore, when treating brain inflammation, doctors must increase the dose of the drug, in hopes that a greater proportion may overcome the hematoencephalic barrier, which operates like a partially impermeable raincoat: if it is only drizzling, it keeps water from getting the person wet, but if it is pouring, a certain amount gets in through the pores of the fabric.

Because of this mechanism, the level of synthetic corticoids in peripheral blood may be substantially different from what reaches the brain. Thus, what doctors estimate as a high dose may actually be high on the periphery but only medium in the brain tissue. As it was the medium doses that increased the inflammatory signaling in the hippocampus and in the frontal cortex, the results may pose a warning of the medical use of these compounds when the target is the central nervous system. Still, further research must be conducted. Munhoz and Scavone plan to soon embark on such research to determine if synthetic corticoids act on the brain in the same way as do natural corticoids. “These data are a warning, indicating that there are variables at play that we still don’t understand regarding how corticoids work,” states Scavone.



Affected cells in bipolar disorder: neurons in green and neuroglia in blue

PATRICK LANDMANN / SCIENCE PHOTO LIBRARY / SPL DC / LATINSTOCK

**Mood changes** - Recently, Scavone began collaborating with Beny Lafer’s team in the Psychiatry Department at the Medical School of USP to identify possible influences of inflammatory processes in the development of psychiatric problems. Lafer is particularly interested in discovering if biochemical changes linked to inflammation may affect the balance of cells and induce their death in individuals with bipolar disorder, which typically causes mood swings between depressive and manic (euphoric) episodes.

Described almost two thousand years ago by Aretaeus of Cappadocia, the most severe form (type 1) of this mental condition (previously known as manic-depressive psychosis) affects approximately one percent of the population. Although it has been treated with relative efficiency in recent decades, its biological origins remain unclear. In the 1990s, international studies identified a considerable reduction in the number of cells (neurons and neuroglia) and a reduction in the cellular protection mechanisms in the brains of bipolar individuals. Associated with inflammation, this cell loss, which becomes stronger during manic

## THE PROJECTS

1. *Stress and intracellular signaling in the inflammation unleashed by LPS in the central nervous system: participation of the glucocorticoids and of the glutamate-NO pathway in the modulation of the transcription factor NF-kappaB* - nº 2002/02298-2
2. *Participation of map kinases, thermal shock proteins and apoptosis pathway in the adverse effects of glucocorticoids upon the central nervous system* - nº 2004/11041-0
3. *Evaluation of the involvement of the Wnt signaling pathway in the physiopathology of affective bipolar disorder* - nº 2008/08191-1

### TYPE

1, 2 and 3. Ordinary Research Grants

### COORDINATORS

1 and 2. Cristoforo Scavone - ICB/USP  
3. Beny Lafer - FM/USP

### INVESTMENT

1. R\$ 191,086.25 (FAPESP)  
2. R\$ 229,197.46 (FAPESP)  
3. R\$ 57,564.57 (FAPESP)

and depressive crises, affects the frontal cortex and possibly the hippocampus as well, which are two of the regions studied by Munhoz and Scavone. Loss or malfunctioning of frontal cortex neurons may help explain patients' difficulties controlling their impulses during manic episodes.

In a review study published this year in the journal *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, Lafer and Scavone proposed a model that attempts to explain how inflammation mechanisms may change the pathway of intracellular signaling activated by Wnt, a protein that regulates the proliferation, migration and specialization of cells. To a greater or lesser extent, all of these processes seem to be jeopardized in mood disorders, such as bipolar disorder and depression. In individuals suffering from these psychiatric problems, strong evidence that something is amiss in the chain of chemical reactions triggered by this protein is the fact that two of the drugs most commonly used to treat bipolar disorder (lithium and valproate) act upon this pathway of intracellular communication, reestablishing the channel of information transmission and eventually avoiding neuron death. "The discoveries about the workings of mood stabilizers have changed the focus of the research from the receptors in the cell membranes and the neurotransmitters that connect with these receptors to what happens in the intracellular world," explains Beny Lafer.

This new way of looking at psychiatric problems, which brought together the teams of Scavone and Lafer, may lead to new treatments. Among the molecules that may become good therapeutic targets for bipolar disorder in the future, Lafer highlights the brain-derived neurotrophic factor (BDNF). Among its many roles, this molecule regulates the survival and ramification of neurons, which are functions that involve Wnt signaling and that are somehow poorly regulated during depressive and manic episodes.

Although it has not yet been determined, there truly appears to be a molecular link between mood disorders, the action of corticoids and the



## AT MODERATE CONCENTRATIONS CORTICIDS INCREASE INFLAMMATION IN THE HIPPOCAMPUS AND IN THE FRONTAL CORTEX

influence of stress. Researchers suspect that this link may be NF-kappaB, which is involved both in the brain response to corticoids and in Wnt signaling, which is altered in bipolar disorder.

In their quest for answers to these questions – and, if possible, new forms of treatment – Lafer and his PhD student, Li Wen Hu, in conjunction with Eliza Kawamoto, are investigating changes in the Wnt pathway. They hope to compare levels of proteins in this biochemical chain in the blood of (1) those with the disorder who have been treated with lithium from the study's outset, (2) individuals with the same condition who have not taken lithium and (3) healthy individuals. To date, they have obtained samples from 20 individuals in the first group, 17 from the second and 36 from the third. "We still don't know whether the dysfunction

of inflammation processes is the cause or the consequence of the episodes of the disease, which improve with mood stabilizers," states Lafer.

The suspicion that corticoids worsen brain inflammation is based on clinical observations. Bipolar patients on corticoids to fight inflammation present a worsening of their psychiatric situation. Moreover, medication for depression that acts contrary to corticoids is currently in its initial trial stage. Although lithium has a different action mechanism to corticoids, researchers do not disregard the possibility that they may act upon intracellular targets in common. Still, it is difficult to know the answer to this question. "It's a complex biochemical waterfall effect, finely regulated by the body in response to stress and to inflammation processes," comments Scavone. "Interfering with this system might unleash consequences that we aren't aware of yet." ■

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### Scientific articles

1. MUNHOZ, C. D. *et al.* Glucocorticoids exacerbate lipopolysaccharide-induced signaling in the frontal cortex and hippocampus in a dose-dependent manner. **Journal of Neuroscience**. v. 30 (41), p. 13.690-8. 13 Oct. 2010.
2. HU, L. W. *et al.* The role of Wnt signaling and its interaction with diverse mechanisms of cellular apoptosis in the pathophysiology of bipolar disorder. **Progress in Neuro-Psychopharmacology and Biological Psychiatry**. v. 35 (1), p. 11-17. 15 Jan. 2011.