

Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

Edo Ronald de Kloet: How does the action of glucocorticoids change from protective to harmful? What is the cause? And what are the consequences?

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Genomic Psychiatry; <https://doi.org/10.61373/gp024k.0088>

Keywords: Psychoneuroendocrinology, pharmacology, stress, brain, cortisol, stress-related disease

For half a century, Edo Ronald (Ron) de Kloet has pursued a fundamental question in neuroscience: how do stress hormones switch from protecting our brain to potentially harming it? After receiving his PhD in 1972 at the University of Utrecht under David de Wied's mentorship, he spent two formative years with Bruce McEwen at Rockefeller University before returning to the Rudolf Magnus Institute. In 1990, he was appointed Professor of Medical Pharmacology at Leiden University, where he discovered how a single hormone – cortisol – could protect and damage the brain through two distinct receptor systems (MR and GR). This finding opened new paths for understanding and treating stress-related mental disorders. His research, spanning over 600 publications, has transformed our grasp of how the brain copes with stress and earned him numerous honours, including the Geoffrey Harris Award (2005), the ECNP Award (2007), and the Golden Emil Kraepelin Medal (2014) for advancing our understanding of depression. Though officially "retired" since 2009, he remains active as an emeritus professor at Leiden University Medical Centre and academy professor at the Royal Netherlands Academy of Arts and Sciences. Recognizing his contributions to science and society, he was knighted in the Order of the Dutch Lion in 2010. Recently, alongside his long-time collaborator Professor Marian Joëls, he received the 2024 Global Stress & Resilience Network Pioneer Award. In this Genomic Press Interview, Dr. de Kloet reflects on his remarkable journey and shares fresh insights into the fascinating world of stress neuroscience.

Part 1: Ron de Kloet – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

My two older brothers obtained a PhD in biochemistry and molecular biology. During their thesis research, I sometimes joined them in the lab, which inspired me to enter a biochemistry program at the University of Utrecht in 1961. After a dull Bachelor's, I became excited when starting my Master's hands-on research by isolating novel bioactive peptides from the sheep pineal gland, even more so during my Endocrinology training at Organon Pharmaceuticals. I learned from Professor Marius Tausk, the director, that "Endocrinology is a concept, an approach, or even a method. Whatever the specific endocrine subdiscipline, topic, or subject, the binding element is the objective: understanding how signals coordinate the processes in cells, tissues, and organs." This sophisticated view of endocrinology intrigued me and a student colleague at Organon so much that we both wanted to apply for an available neuroendocrinology PhD position guided by the famous Professor David de Wied. However, since we did not want to compete, we did it by flipping a coin. My colleague won and got the position, and I was left empty-handed!



Figure 1. Edo Ronald de Kloet, PhD, Leiden University Medical Centre, The Netherlands.

A month later, I arranged an appointment with Professor de Wied. I related the coin-flipping story on Thursday, 28 November 1968, at 9.00 am. Then, after some discussion, Professor de Wied said: "I'll call the Director of Organon." After 5 minutes, the call ended, and De Wied said, "You can start this coming Monday, 2 December, at Organon with a PhD project." He also defined the topic of my thesis. Bruce McEwen had just published his hallmark paper on the retention of tracer amounts of ³H-corticosterone in cell nuclei of the hippocampal pyramidal and dentate gyrus neurons. De Wied said, "We can do this better, Ron! We will examine the central action of the much more potent glucocorticoid dexamethasone."

After two years, I wrote Bruce a letter stating that I could not reproduce his finding of corticosterone binding in the hippocampus with





dexamethasone, and he invited me over to New York to solve the issue in his lab. As a postdoc in Bruce's lab, we confirmed the inability of dexamethasone to label the corticosterone receptors in the hippocampus. Only 20 years later, using mouse mutants obtained from Piet Borst, we found out why: Dexamethasone, rather than corticosterone, is a substrate for multidrug resistance P-glycoprotein (mdr-Pgp) in the blood-brain barrier, which pumps the synthetic steroid out of the brain! Instead, dexamethasone acts in the anterior pituitary corticotrophs to suppress stress-induced ACTH release, a fundamental finding for understanding the Dexamethasone Suppression Test, a laboratory test assisting in the diagnosis of depression, further developed into the Dex/CRH test by my colleague Florian Holsboer in Munich.

I learned that (i) luck requires a prepared mind, (ii) partial reinforcement extinction works, and (iii) one needs patience.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channelled you toward that leadership responsibility?

The second phase in my career started with my tenured appointment in 1975 as Associate Professor at the Rudolf Magnus Institute under De Wied's guidance upon returning from Rockefeller University. The staff position required the development of a neuropharmacology teaching program in biomedical sciences and participation in the Institute's research on neuropeptides. The term 'neuropeptides' was coined in the late sixties by David de Wied to define the central effects of fragments of vasopressin, oxytocin, and ACTH that were devoid of their classical endocrine activity. For instance, the fragment vasopressin (4-9), the "memory pill", reinforced memory consolidation of fear-motivated behaviour.

The late '70s were exciting times for neuropeptides! With Eva Mezey and Dan Dorsa, we showed that peptides cleaved from pituitary hormones could reach the brain via retrograde transport in the pituitary stalk and the perivascular space. With Peter Burbach, we identified the brain endopeptidases that generated vasopressin, oxytocin, and ACTH-derived neuropeptides from larger precursor molecules. Miklos Palkovits taught me in the mid-70s neuro-anatomy and the ability to punch more than 100 different nuclei from frozen brain sections (600 punches/hour), serving many other research groups.

In 1984, with Anat Biegon, Door Voorhuis, and Jack Elands, we discovered the distribution of oxytocin and vasopressin receptors in discrete rat brain regions using in vitro autoradiography. That discovery culminated in an exciting twist in the songbird: testosterone-induced vasotocin receptors were concentrated around a song nucleus in the canary brain (*n. robustus archistriatalis*). Stimulation of these receptors modulated the development of the stereotyped canary song.

I learned that to grow toward a leadership role in neuroscience, you need to collaborate with experts in research on various layers of biological organization, from molecules to cells and circuits to behaviour. While the above experiences were exciting, the real breakthrough toward leadership was understanding how glucocorticoids act, as detailed in the next section.

Please share with us what initially piqued your interest in your favourite research or professional focus area.

In 1985, we had a "Eureka" moment in recognizing the identity of the rodent hippocampal corticosterone receptors. At that time, Roussel Uclaf had synthesized a 'pure' glucocorticoid, distinguishing between mineralocorticoid receptors (MR) that bind corticosterone with a 10-fold higher affinity than the classical glucocorticoid receptors (GR). With Dick Veldhuis and Hans Reul, we realized that the tracer doses of ³H-corticosterone provided a sufficient amount to occupy the MR but not the GR. For GR occupancy, corticosterone concentrations must increase to levels circulating around the circadian peak or after stress. With Hans Reul, Anke van Eekelen, and Win Sutanto, we published the distribution of MR and GR in the rat brain using in vitro autoradiography, immunocytochemistry, and in situ hybridization. With Chris Edwards from Edinburgh, we demonstrated that the enzymatic breakdown of naturally occurring glucocorticoids was essential for the MR to become aldosterone-specific in epithelial cells such as the kidney.

With an understanding of the complementary MR- and GR-mediated actions of corticosterone and cortisol, we mined gold. Suddenly, we knew how to design experiments that made biological sense in stress research—the Eureka moment triggered an avalanche of studies. It provided the in-road to the group's transition to Leiden University in 1990, the Division of Medical Pharmacology, with my promotion to full Professor at the Leiden/Amsterdam Centre of Drug Research (Leader Douwe Breimer). In neurophysiology, we had an intense collaboration with Professor Marian Joëls at the University of Amsterdam, who discovered MR and GR's complementary role in regulating transmitter responses and ion conductances in a U-shaped relationship: MR activation transiently increased hippocampal excitability, which was suppressed, subsequently, by stress-induced GR activation. Marian Joëls and Henk Karst discovered in 2005 that MR can also mediate rapid non-genomic actions in the hippocampus.

With Anna Ratka, we showed the physiological role: MR activation is essential for the tone and activation of the stress response system, while subsequent GR activation facilitates suppression by negative feedback. In behaviour, Melly Oitzl found that MR is necessary for retrieving information and selecting a coping style, while GR activation promotes memory consolidation. Menno Kruk made a case for MR-dependent anxiety/aggression-driven phenotypes. Nicole Datson pioneered gene expression profiling in laser-dissected brain regions and identified numerous novel glucocorticoid-responsive pathways in the brain under stress, particularly in epigenetic processes. Erno Vreugdenhil discovered a glucocorticoid-responsive neuroplasticity gene doublecortin-like kinase, which functions in microtubules during development and neurogenesis. With Seymour Levine, we made significant contributions to the role of glucocorticoids in programming stress-coping and adaptation in neonates for later life.

Thus, a 1968 PhD project developed into a successful research program. I learned that focus, collaboration, and mutual respect are the ingredients for an exciting scientific journey. Melly, Menno, Erno, Nicole, Onno Meijer, and Roel de Rijk formed, as group leaders, a dream team, guiding together more than 200 Master's and PhD students, postdocs, guests, and technical and administrative staff, each delivering a unique contribution that I cannot highlight due to space limitations. See for a summary of the first 30 years of my career in David de Wied's Festschrift: de Kloet ER. Stress in the brain. Eur J Pharmacol. 2000;405:187-198.

What impact do you hope to achieve in your field by focusing on specific research topics

2009 I reached emeritus status, but I had enough grant money to continue for five years before the Dutch mandatory retirement at 70.

Collectively, we have contributed to the knowledge of how cortisol coordinates body and brain function to support coping and adaptation and how the hormone programs this adaptive response for life. We formulated the MR: GR (im)balance hypothesis: "Upon imbalance of the MR and GR-mediated actions, the stress response's initiation and management becomes compromised. At a certain threshold, this may lead to a condition of neuroendocrine dysregulation and impaired behavioural adaptation, which potentially can aggravate stress-related deterioration and promote vulnerability."

We collected data (and are still doing so) to test this hypothesis. Two out of several highlights. Firstly, Roel de Rijk and Liane Klok discovered an MR haplotype associated with optimism that protects against depression. This discovery earned US and EU patents as signs of a successful translational opportunity. Secondly, Onno Meijer became my successor in Leiden and continued to work on glucocorticoids developing, with the support of Corcept Therapeutics, novel Selective Glucocorticoid / Mineralocorticoid Receptor Modulators (SGRM / SMRM) targeting tissue selective receptor co-regulators. With this prospect, glucocorticoid therapy will have fewer side effects.

Please tell us more about your current scholarly focal points within your chosen field of science.

I was fortunate to participate in the exciting projects of Alex de Nicola's group (Buenos Aires), which has been pioneering the striking ability of SGRM and SMRM to reverse neuropathology in animal models of chronic



Figure 2. Ron de Kloet sailing Nordic Folkboat VoiVoi.

stress, hypertension, and neurodegenerative diseases. Some of these Corcept compounds are now in phases 2 and 3.

I am happy to participate in a challenging program led by Megan Galbally (Melbourne, Australia), who explored the prevalence of childhood anxiety disorder in the offspring of mothers from the Mercy Pregnancy Emotional Wellbeing Study, a longitudinal cohort study of pregnant women exploring the impact of perinatal depression (from conception to birth) at delivery, and 6 months, 12 months, and 4 years postpartum. The outcome of these exciting studies aligns with developmental animal studies: stress during early life programs via cortisol action in the amygdala emotional reactivity for later life.

I occasionally write a commentary or review on stress. For instance, with Marc Molendijk, we wrote a series of articles on anthropomorphism in neuropharmacology, using the forced swim test as an example.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

Examining a fundamental neuroscientific question requires a multidisciplinary approach in a social, behavioural, biochemical/molecular, and physiological context. Keeping up team spirit requires frequent meetings to discuss progress. Team spirit and social lab life go together: joint coffee breaks, lunches, sports, and 'cabaret' are essential for shaping collegial trust and passion.

At Genomic Press, we prioritize fostering research endeavours based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

I support the European 'Agreement on Reforming Research Assessment'. This agreement between the European Commission, Science Europe, and

the European University Association (EUA) endorses the objectives of our National Recognition & Rewards program. The agreement focuses on recognizing and rewarding academics for their various tasks. This focus implies that research assessment primarily occurs through a qualitative evaluation rather than based on the number of publications, h-indices of authors, or journal impact factors. See <https://recognitionrewards.nl/2022/10/10/dutch-knowledge-institutions-sign-european-agreement-on-reforming-research-assessment/>.

What do you most enjoy in your capacity as an academic or research leader?

To inspire students about the beauty of the brain, from genes to behaviour, in all imaginable contexts, discuss in-depth new findings, and guide young scientists in the first years of their scientific life.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

I have a semi-professional online weather station called 'The Hippocampus,' in a polder 4 m below sea level close to where I live. Just a few highlights: I could measure the air pressure changes and wind shifts following the January 2022 Pacific Hunga Tonga-Hunga Ha'apai submarine volcano outburst. I like ice skating, swimming, sailing, hiking, and gardening.

Part 2: Ron de Kloet – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

I realize that happiness is context-dependent, and here are some ingredients. During exercise, my endorphins work; during social life, oxytocin may peak; if I compete, dopamine helps to pursue success; and serotonin gives a sense of control during stress. It is all perfect if it works.

What is your greatest fear?

The feeling that I have no control.

Which living person do you most admire?

I admire my brother for saying, "Doing nothing is not an option," and he succeeded in extending the high-quality life of one of his beloved sons for another 8 years.

What is your greatest extravagance?

To keep my 65-year-old mahogany wooden Nordic Folkboat in excellent shape.

What are you most proud of?

In my scientific life, I am most proud of my 57 PhD students, who all successfully defended their thesis.

What is your greatest regret?

I should have reserved more time for social activities and reading.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



What is the quality you most admire in people?
Sense of humour, reliability.

What is the trait you most dislike in people?
Narcissism

What do you consider the most overrated virtue?
In science, when an individual's h-index is a criterion for judging scientific quality and a predictor of future performance and success.

What is your favourite activity?
A daily hike of an hour is inspiring and gives a good feeling.

Where would you most like to live?
Rural environment, at a lakefront, with Dutch weather.

What is your most treasured possession?
Science-related: my 1000+ hippocampus items.

When and where were you happiest? And why were so happy then?
Again, context-dependent. An example: February 1996, Wengen, Switzerland. We rented a cottage and went skiing and hiking; the weather was fantastic, and there was a silent and impressive red evening sun on the 4000m high mountains. Alternatively, sailing or wandering with Marian through nature, or understanding experimental data.

What is your current state of mind?
Quiet, but with a sense of urgency for things to do

What is your most marked characteristic?
Interest in the other person, what they do, how they think.

Among your talents, which one(s) give(s) you a competitive edge?
In science, to identify talent that can synergize in a multidisciplinary fashion to reach a common goal.

What do you consider your greatest achievement?
With my associates' help, we have provided evidence to substantiate that cortisol action controls a switch between resilience and vulnerability in adaptation to chronic stress.

If you could change one thing about yourself, what would it be?
Be more creative in thinking out of the box.

What do you most value in your friends?
Integrity.

Who are your favourite writers?
John Grisham's detectives, Marten Toonder's 177 Bommel stories, Val Howells's 'Sailing into Solitude,' and Marian Joëls' latest book, "Finished," (ResearchGate), a novel about the world of science, confronting and written with compassion and wit.

Who are your heroes of fiction?
Kwetal, a subterranean dweller and mastermind, is my hero in the 38th story from the Bommelsaga, written and drawn by Marten Toonder. Kwetal coined the term "Denkraam" (no English translation) to describe the brain.

Who are your heroes in real life?
Herman van Praag (1929-). I attended the presentation of his latest book (November 2024) a few days before this interview. Entitled: Gemoedsbewegingen (emotional movements). Professor Herman van Praag founded Biological Psychiatry in the Netherlands. My other heroes passed away.

What aphorism or motto best encapsulates your life philosophy?
"As 't net kin sa't moat, dan moat 't mar sa't kin". It is from the Frisian language, where my roots are. In English, it would be something like: "If it cannot be done as it should be, then it should be done as it can."

Leiden, The Netherlands
25 November 2024

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Funding Sources
This article was not supported by external funds.

Author Disclosures
The author declares that no conflict of interest exists.

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