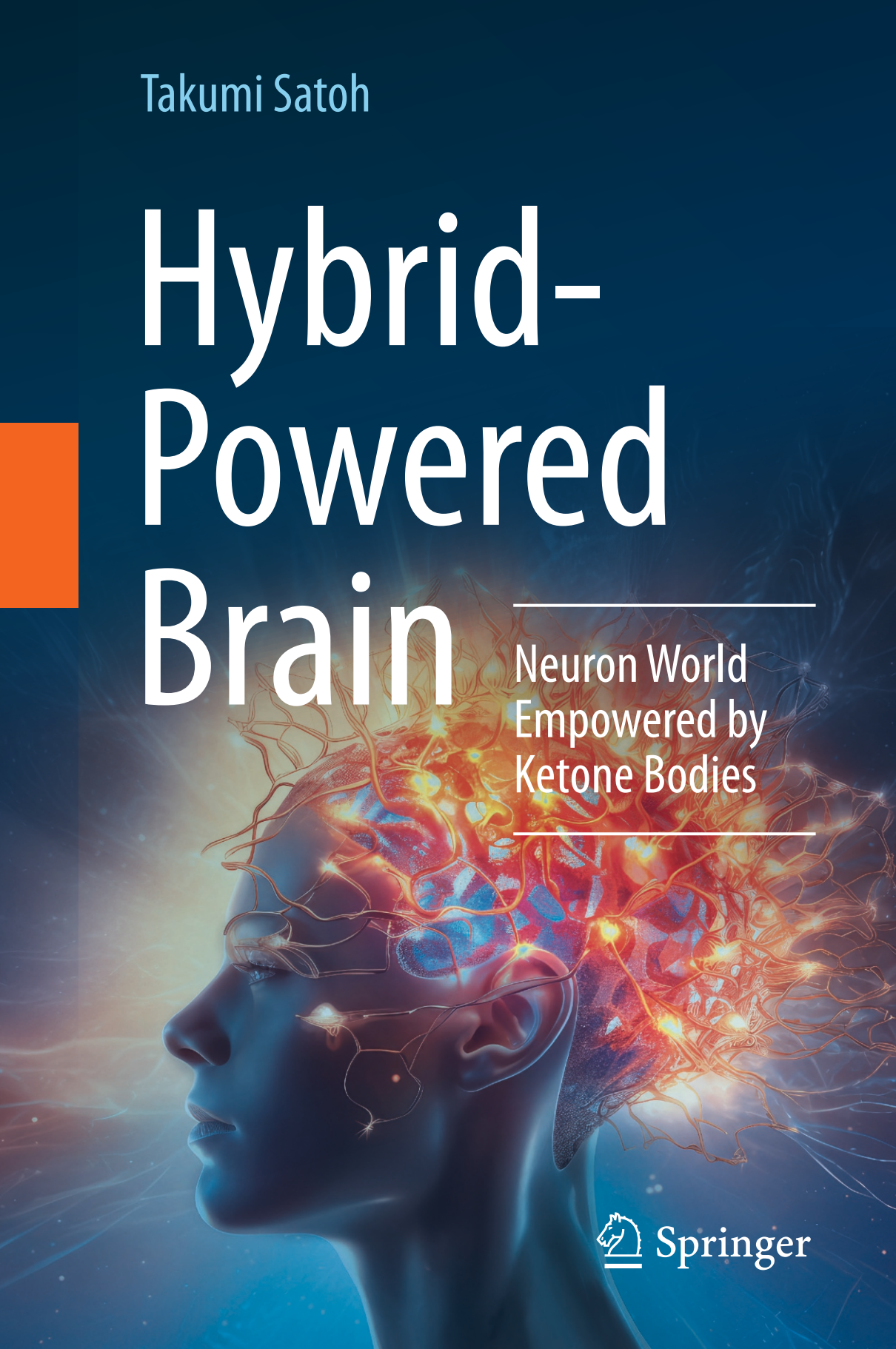
Takumi Satoh

Hybrid-Powered Brain

Neuron World Empowered by Ketone Bodies



Springer

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ISBN 978-3-031-54149-0 ISBN 978-3-031-54150-6 (eBook)
https://doi.org/10.1007/978-3-031-54150-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to my wife, Chiaki Satoh.

I have been happy just because She is with me.

Preface

Days of Kyoto University

I was a graduate student at Kyoto University [1988–1992] when I saw the then-President of the USA, George H.W. Bush on his way to sightseeing the Kyoto Imperial Palace in 1992. Then, I lived in an apartment in the Sakyo Ward and remember that the host lady always complained about her son's eating habits. He had just a cup of coffee for breakfast and had some meat for dinner. She worried continuously about his health and wished that her son ate carbohydrates, such as rice, in the morning.

Since she always took care of me, I wished to solve her worries. The next weekend, I went to her house after having bought a book written by a famous doctor. Opening the lattice door, I said to her "Breakfast without carbohydrate seems harmful to all persons. It is glucose that is supplied as an energy substrate to the brain. It is highly advisable to have rice or bread in the morning. This is a basic condition for the brain to have high performance. In addition, this is a comment of a famous person." She gently stroked the book with her hands, wearing a large green–blue opal ring, and said "Thank you so much. I will certainly read this book." This is one of the most impressive memories with my benefactors.

Not only the author of that book, but most people all over the world, believed that the brain does not work without glucose. This superstition has spread widely back then, and even now many people believe this. However, 30 years passed since this time. At that time, we had to change the code of the fixed telephone to send mail, but now an e-mail can be sent from the train within several seconds by hand unless you worry about hitting the face of the next person. Thus, we have come to a time when this common sense has to be revised from "glucose is the only source of brain energy." We must repaint the wall before big cracks, namely "common sense is only correct if blood glucose levels are stable."

Days of Neuroscientists

I will return to the story here when I was young. After I completed graduate school at Kyoto University and began to work in a pharmaceutical company, I realized that I was not a business person. Many friends had warned me that I was not a suitable

businessperson, but 3 years had passed since I realized this. At last, I decided to return to being a researcher and searched for a position. I soon met Prof. Hiroshi Hatanaka at the Graduate School of Osaka University. He was then a famous professor of neuroscience in Japan and had completed writing the book "Brain as Material." When I met him, I took the first step toward becoming a neuroscientist. Since then, I have studied neuroscience for over 25 years. I have been walking with neurons in the brain. This is the system by which we can understand, by which we see and hear, by which we can remember what we think and feel, and by which we can choose what we like. The most interesting thing I ever felt was the system of finalizing life, named "neuronal death."

I moved to my present position 10 years ago, where I was determined to study the antiaging of the brain in terms of energy substrate as an emerging topic. At that time, I had the impression that few researchers were dealing with this topic. Ten years have passed, and I am writing this book. After 30 years as a researcher, my desk is full of information obtained from papers and books on neurons. In addition, I have a wealth of information from papers and books studying antiaging. They are mixed and fermented; some are simmering. Now, using gloves, let's pick out the bundle of paper processed to a heat-resistant temperature of 120 °C.

The following concepts emerged from the "steam."

"When blood glucose is not stable, neurons will be energy deficient. In the worst case, neurons will die. At least, they will not have their usual performance. The power to eliminate waste and impurities will decrease. The present problems of depression and Alzheimer's disease should be considered in terms of energy deficiency."

"If left unattended, the number of synapses, which are required for communication between neurons, will decrease. However, people can deal with energy deficiency on their own without dependence on any drug."

"When the brain cannot use glucose, it can function by using ketone bodies as an energy fuel. With this alternative, neurons can achieve much better performance, greater brain blood flow, greater capacity for clearance, and more efficient receptor systems."

Why I Wrote This Book?

I want to keep these boiled paper bundles properly before they disappear beyond oblivion. This is why I wish to publish this book worldwide. I will have less than 5 years before I retire from this position. A compound named "ketone bodies," which now are beginning to attract people's attention, are now facing the danger of being completely forgotten although ketone bodies, a group of compounds, are one of the most important energy fuels for the human brain.

I chose the two issues as the main topics of the book from the scientific point of view.

1. It is highly advisable to deal with the brain diseases of depression and dementia when the symptoms remain within energy deficiency. It is certainly possible to keep the progression much slower than the issues are left unattended. The one

energy substrate is certainly glucose, and the others are ketone bodies. If we properly use both glucose and ketone bodies, it is helpful to keep the brain at high performance for an extended period. For people to understand the brain energy problem properly, my possible task is to provide simple explanations of the brain energy system and to show the direction of eating habits for supplying brain fuel.

2. Big brain per body size is the most striking physiological feature of human beings. Why do they have so big brains? There are many possible answers to this issue according to their expertise. However, as far as I know, there is no available answer to what energy-producing systems supply the developing brain. Big names in biology must be thinking on this issue, but no person has reached a simple answer. By considering these backgrounds, I will try to provide you with a simple and scientific explanation of the following issues. By focusing on these two issues, I have determined to explain the important roles of glucose and ketone bodies.

   (a) Why did human beings come to have a big brain?
   (b) What energy system supply developing brain energy fuel? Which is more important for the brain, glucose or ketone bodies?

I am sure that most people, who will take this book, can read this book to the last page since I arranged the book so that readers can understand hypothesis as hypothesis and fact as fact.

Hachioji, Japan Takumi Satoh

Goal of the Book

The world has been experiencing a great paradigm shift. We are shifting from "Expanding Society" to "Sustainable Living." However, we have not innovated yet a simple methodology to allow the brain to be sustainable and work well for our lifetime. "Sustainable Brain" is one of the most important elements of "Sustainable Living." Here I am going to propose a Practice for "Sustainable Brain." This book is aimed at "Sustainable Brain" by hybrid power of glucose and ketone bodies. Small Ketogenic is the most essential key to starting up this hybrid-powered brain.

Summary of the Book

To maintain positive feelings or sustain a fulfilling mood throughout the day, the priority is to send energy substrate to the brain. Since neurons have high energy demand, they are affected by energy shortage. The hybrid system of glucose and ketone bodies is the most effective method to preserve cognitive functions at high levels. In addition, hybrid power to the brain may help to maintain good cognitive function in older people. This is termed a "small ketogenic," which induces a slight increase in ketone bodies (0.2–0.5 mM). People can easily maintain the daily concentrations of ketone bodies by slight changes in eating habits. For example, it may be necessary to extend intervals between meals and allow the feeling of slight hunger to develop. This range of concentrations of ketone bodies is sufficient for keeping the brain calm and constitutively active.

Highlight 1: Hybrid-Powered Brain
To keep a positive feeling or spend the day in a fulfilling mood, the priority is to send out energy substrate to the brain. The active brain requires a supply of enough energy substrate to the brain. Neurons full of energy allow your feelings to become sharp, and your judgment is clear. On the contrary, how is the brain working under energy shortage? Since neurons have high energy demand, neurons are greatly influenced by energy shortage. Especially, low blood glucose may cause serious effects. When blood glucose levels are moving up and down in daily life, the serious problem is not high glucose, but low blood glucose because the brain is exposed to energy shortage. The brain finds it difficult to open the memory drawer. Feelings sink, and anger and sadness grow stronger. Everything may start to flow backward. To avoid these situations, it is worth considering the brain energy system that you don't usually care about and creating a chance of thinking about your brain.

Highlight 2: Small Ketogenic
Homo sapiens has two systems of brain energy. Glucose is produced from carbohydrates and ketone bodies are from fat. The two systems can compensate for each other. It is very easy to start up this hybrid system. You may have to extend the interval between meals and have time to feel small hunger in daily life within a reasonable range. This is called "Small Ketogenic." The hybrid system of glucose

and ketone bodies is the most effective method to preserve cognitive functions at high levels. The hybrid-powered brain may contribute to the mentality of the old people in the village of longevity. They are enjoying daily life and farm working under these mentalities. The target range of concentrations of ketone bodies may be 0.2–0.5 mM. The range of concentrations of ketone body is sufficient for keeping the brain calm and constitutively active. We can attain healthy longevity by improving eating habits to very slightly (0.2–0.5 mM) termed as "Small Ketogenic." The big advantage of "Small Ketogenic" is to continue as long as we are alive. This eating habit does increase ketone bodies, but the increase is very small. The possible solution of ketone body concentrations (0.2–0.5 mM) is that anybody easily keep every day. This is why the author assumes that the Small Ketogenic (0.2–0.5 mM ketone body) empowers the brain and induces sufficient health effects.

Tutorial to Reader

It is an author's honor if you feel more familiar with your brain for high performance when you read this book. While reading this book, I am confident that surprising functions of the human brain may attract your brain.

1. All of the materials I have mentioned on the functions and structures of the brain are based on scientific papers.
2. There are many cases where "parables" and "personal impressions" are included in the text and enclosed within parentheses. These sentences shown by *"( )"* are inserted because scientific and formal statements can be easily understood. When you do not need to read these informal paragraphs enclosed within parentheses, these can be skipped.
3. Please feel free to read the *"Attention"* (a trivial with a cartoon) at the end of *Chapters 1–5*.
4. *References* are added to show scientific papers for readers to easily access to origins of knowledge. References are marked as *"[ ]"* such as *[51]* and *[45]* in the *Text*, *Figs*, and *Tables*. Please refer to these documents if you are interested in the original scientific data.
5. The main topic of this book is neuroscience but not eating habits. Thus, information on eating habits is highly limited. By using this book, I would like you to reconsider your brain energy for high performance in your work.
6. Ketone bodies, comprising three compounds (3-hydroxybutyrate (3HB), acetoacetate, and acetone), are considered alternative energy substrates when glucose is unavailable to the tissues. Since 3HB occupies over 85% of ketone bodies in the systemic circulation, 3HB may be described as "a ketone body." I will use both ketone bodies and 3HB in this book. In the physiological context, "ketone bodies" are often used. In addition, "3HB" is often used in the pharmacological context.
7. Since I am not a native speaker of English, plain English is used here.

Acknowledgment

Dr. Koujiro Tohyama, a former professor at Iwate Medical College, is appreciated with much respect and deep gratitude as he gave me many valuable photographs and clear neuroanatomical forward comments (*Figs. 1.2, 1.3, 1.4, 1.6, 1.7, 1.8, 1.9, 1.13, 5.1, 5.2, and 6.6*). It is my good luck to have his specialist input. He continues to research in the field of neuroanatomy at a high level. In particular, the first chapter would not be possible without his details.

My wife has always been with me and has provided me with many valuable comments. I desired to write clear comments in this book, but she warned me that the comments should be in a moderate tone. In addition, she asked detailed questions as a representative of the readers about the explanations that I thought were OK. Although I thought it was troublesome, many comments have now become understandable, so that readers can easily grasp the essence of their meaning.

Mr. Fumiyuki Minami presented illustrations of unique characters that added punch to the dishes finalized by cooperation. All characters are required, although the character that I like best is Miss Betz. I am grateful to the illustrator and like all of his characters.

Of course, I have unspeakable gratitude for Mr. Alexis Rivas (Springer), the editor of this book. This book can be published after a meeting with an excellent editor. He caught me at the tip of the antenna with that keen sensitivity and approved the publishing of a book.

Finally, I am very grateful to a certain person in the USA. This person is Prof. Stuart A. Lipton, who lives in La Jolla, California, a place famous for surfing and a wonderful town with many friendly people. He was running a large laboratory (Del E. Webb Center for Neuroscience) at the Burnham Institute, one of the top 10 institutes of all facilities in the USA. (Now he is a professor at the Institute for Translational Research in the Scripps Research Institute, right next door to the Burnham.)

Twenty years ago, while pursuing the identification of a receptor of NEPP11, a synthetic probe, I wrote an email to Stuart. Back then, he was studying the biological significance of S-nitrosylation, a mode of protein modification. He is known as one of the individuals who discovered memantine, one of the most famous

antidementia drugs. At the time, I contacted a potential Nobel Prize candidate without thinking too much. Five minutes later, I got an answer, and 6 days later, I was alone standing at the Narita Airport to visit La Jolla for an interview. Then, I stayed in his laboratory for over 2 years. I was embraced by his considerably speedy English and had to adjust to his tight experimental schedule. He lived in a big mansion with his family and valued time with them. He returned home at a fixed time in the evening. Although I visited his office to discuss my ideas, he appeared not to listen to my uncertain guesswork and looked as if he was not interested in it. He never talked about wishful thinking or vague predictions. Just for that, I did not see the moment the light shone in his eyes and his mouth became relaxed as he talked. Several months later, we published a coauthored paper in *Proceedings of the National Academy of Science*. He was always working hard and deep in thought about something. But when I took my family to his lab, he was smiling and cheerful, like another person, and that is one of my modest memories of La Jolla. I learned my passion for research from Stuart. Thanks to him, I can talk about the surprising functions of the brain.

We were introduced to the wonderful daily life in La Jolla by him. My and my family's numerous pyramidal neurons of the neocortex have been deeply engrained with uncountable memories of relaxing time on the terrace of cafés on a Sunday morning and the vivid, colorful bundles of flowers that are always for sale in the morning market. To preserve these valuable memories until I am dead, I wish to continue the eating habit that activates the hybrid system of glucose and ketone bodies for the brain. My wish is that all the cells in my brain would preserve the memories of the seven-colored sky and sea that we saw at the Del Mar beach and the experience of California that we had, such as other small memories, including the smell of soy sauce.

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