Chapter 3
The mechanism of cephalic hypersensitivity syndrome:
Theoretical predictions from observations

As you will know after reading Part 2, the symptoms commonly experienced by the patients who attend my clinics include headache, stiff shoulders, dizziness / vertigo, numbness in a limb, and insomnia. Often they have been suffering for a long time, having undergone tests at several different hospitals without any cause having been discovered, and some have been told "There's nothing wrong with you." Dictionaries define "indefinite complaint" as "a state in which patients complain of a range of subjective symptoms despite no apparent organic disease being present" (Kojien) and "complaints of vague physical illness that do not constitute a specific disorder. These may include heavy-headedness, being easily tired, and lack of appetite" (Digital Daijisen). Over many years of facing up squarely to the complaints of such patients and engaging in their treatment, I have come up with the following three hypotheses.

Hypothesis 1: Many of the chronic illness syndromes suffered by patients are caused by cephalic hypersensitivity syndrome.

Hypothesis 2: Cephalic hypersensitivity syndrome can be explained in terms of the molecular biology of synaptic plasticity.

Hypothesis 3: A biopsychosocial model is appropriate for the treatment of cephalic hypersensitivity syndrome.

These hypotheses have yet to be fully scientifically investigated, but some scientists have proposed similar concepts, and findings that back up my theories have been published. The greatest support for them is the fact that patients are actually cured, but here I will describe some of the arguments that have been suggested at this stage.

1 Hypothesis 1: Many of the chronic illness syndromes suffered by patients are caused by cephalic hypersensitivity syndrome

Yunus' concept of Central sensitivity syndrome (CSS)

Muhammad Yunus, a professor in the Division of Rheumatology of the University of Illinois College of Medicine in the United States, has proposed the concept and the term of central sensitivity syndrome (CSS) on the basis of his treatment and studies of fibromyalgia and rheumatism patients. Although we come from different standpoints, mine as a neurosurgeon and neurologist and his as a rheumatologist, and I identify the complaints of patients who experience "pain" in the broadest sense as the common denominator, whereas Yunus emphasizes the symptoms of fibromyalgia, we are both following similar trajectories. However, Yunus' concept of CSS is not described in the Japanese Fibromyalgia Guidelines 2013, and I will therefore summarize its important points here.

① Definition of central sensitivity syndromes

Yunus defines central sensitivity syndromes as a group of illnesses that meet the following two conditions[1]. The figure shows the current conceptual diagram of CSS.

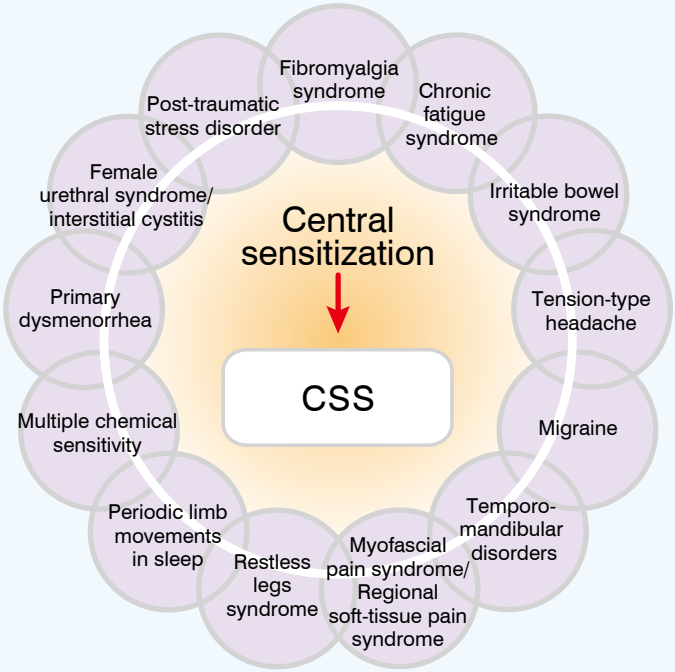
(a) Mutual associations between the CSS members

(b) Presence of central sensitization

Mutual Association

Yunus carried out an in-depth study of the commonalities between the various different central sensitivity syndromes, focusing mainly on fibromyalgia patients, and summarized the results. Based on this investigation, there are currently 13 syndromes accepted as central sensitivity syndromes, including some with symptoms that are obviously associated in clinical terms even though research studies have yet to establish sufficient evidence and that further research is expected to substantiate[2]. This is why the legend to the conceptual diagram emphasizes that it shows the disorders and syndromes that are “currently” classified as CSS, as it is possible that more may be identified as belonging to this category in the future[1–3].

Currently proposed members of the CSS family
with overlapping relationships and
a common pathophysiological link of central sensitization



Source: Figure 1 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):341.

Presence of central sensitization

Central sensitization refers to the development of hypersensitivity not only to uncomfortable stimuli such as pressure and heat, but also to touch and other stimuli that are not normally uncomfortable[2]. In terms of clinical signs, it appears as the amplification of pain from heat, mechanical stimuli, and other types of stimuli, hyperalgesia, and the spread of pain and uncomfortable sensations, all of which become chronic. Central sensitization is defined as the hyperexcitation of the central nervous system, and the aforementioned symptoms appear after peripheral stimuli as a result of the alteration of sensory processing. The table shows the neurochemical substances and neuroreceptors involved in central sensitization.

Neurochemicals and neuroreceptors involved in central sensitization

Neuromodulators/neurotransmitters released by activated C-nocireceptors presynaptically	
Substance P (SP)	Somatostatin
Calcitonin-gene-related peptide (CGRP)	Galanin
	Nerve growth factor
	Glutamate
Vasoactive intestinal peptide (VIP)	Aspartate

Post-synaptic neuroreceptors/neuroeffector targets	
Neurokinin 1 (NK1)	Metabotropic glutamate (mGlu)
N-methyl-D-aspartate (NMDA)	Tyrosine kinase B (Trk-B)
Alpha-amino-3-hydroxy-5-methyl-4-isoxaloeproprionate (AMPA)	Protein kinase gamma (PKC-gamma)
	Vanilloid subfamily (TRPV-1, TRPVL-1)

Source: Table 1 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):342.

Substance P causes secondary nerve excitation and the expansion of regions of pain that is characteristic of central sensitization. The release of neurochemical substances such as substance P, nerve growth factor, and glutamate overexcites the synapses, resulting in the release of the magnesium block on NMDA receptor channels. The activated NMDA receptors increase intracellular calcium inflow, which causes changes in the cell membrane and activates protein kinases, phospholipases, nitric oxide synthases, and other enzymes that have a major effect on central sensitization. This series of reactions results in neuroplasticity. Substances including dopamine, serotonin, noradrenaline, GABA, enkephalin, and adenosine are all involved in central sensitization[2].

- **Central sensitization is the common factor in central sensitivity syndromes (CSS)**

Yunus mentions the following evidence of central sensitization for 12 of the 13 disorders and syndromes shown in the figure, with the exception of periodic limb movements in sleep[2].

- **Fibromyalgia**

Patients exhibit a generalized exaggerated pain response by digital pressure. They are reportedly hypersensitive to a range of stimuli [including heat, cold, electric, quantitative sensory testing (QST), and sound]. Central sensitization has also been suggested in fMRI and EEG studies of response to stimuli.

- **Chronic fatigue syndrome**

Many aspects remain unknown. A study of chronic fatigue syndrome patients, of whom nearly half had myalgia, demonstrated hypersensitivity to electric stimuli, but not in the overlying skin or subcutaneous locations.

- **Irritable bowel syndrome**

Discomfort in the lower abdomen and lower back are the two main markers of central sensitization. Most studies have used balloons as a stimulus, but central sensitization has also been demonstrated by using heat and electric stimuli. Patients with irritable bowel syndrome exhibit both rectal and cutaneous allodynia. Central sensitization has also been suggested in fMRI and PET studies of rectal and cutaneous stimuli.

• **Tension headache**

A facilitated spinal nociceptive flexion reflex was evident in response to stimuli (pressure or heat) in both cranial and extracranial sites. Central sensitization was also shown by cerebral-evoked potential and a deficient pain inhibitory response by a diffuse noxious inhibitory control mechanism. However, a lack of central sensitization has also been reported by cutaneous heat and electric stimuli.

• **Migraine**

Enhanced sensitivity to stimuli (mechanical, heat, cold, CO_2 laser) has been demonstrated in both cranial and extracranial sites. Hypersensitivity to sound and light has also been shown. Cutaneous allodynia on the forearms and around the eye sockets is also evidence of central sensitization.

• **Temporomandibular disorders**

Temporomandibular disorders represent a heterogeneous group of disorders in patients with or without structural pathology. Only the myofascial variety by Research Diagnostic Criteria is included as a central sensitivity syndrome. Hyperresponsiveness to both facial and extracranial stimuli (pressure, heat, ischemia, and hypertonic saline) has been recorded.

• **Myofascial pain syndrome/regional soft-tissue pain syndrome**

Yunus *et al*. regard these two syndromes as constituting the same entity. In both, hypersensitivity to stimuli is evident at both symptomatic and distant sites. Amplified responses to pressure, heat, cold, electric stimulus, and vibration are present.

• **Restless legs syndrome**

Punctate stimulation by pin prick reveals generalized hyperalgesia in the arms and legs.

• **Multiple chemical sensitivity**

Multiple chemical sensitivity is a time-dependent sensitization that elicits central sensitization as the result of repeated exposure to environmental chemicals. Although there is almost no experimental evidence other than noise sensitivity, studies of other central sensitivity syndromes exist that show similarities with chemical sensitivity.

- **Primary dysmenorrhea**

Patients with dysmenorrhea exhibit lower thresholds for stimuli (pressure, heat, and electric stimulus) in the abdomen, back, and extremities during menstruation.

- **Interstitial cystitis**

Sensitivity to bladder distension with physiological saline and muscle pressure increases.

- **Post-traumatic stress disorder**

Like temporomandibular disorders, the mechanism of sensitization is still at the hypothesis stage. It is believed that sensitization is induced by emotional stress rather than chemicals. Further studies are required.

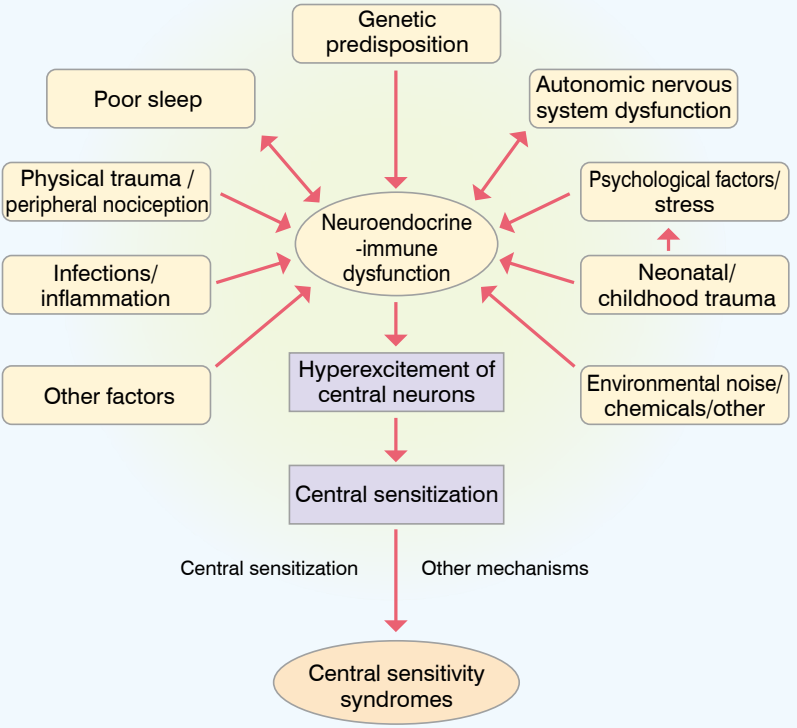
- **Depression and other mental disorders**

Many studies have shown that patients with central sensitivity syndromes also suffer from depression or other mental disorders. The relationship between pain and depression is a complex one, however, with many different factors involved, and there is insufficient direct evidence for central sensitization to sensory function in depression. Depression is associated with all the disorders classified as central sensitivity syndromes, but overlap does not necessarily mean total overlap. Studies on anxiety and panic disorder are extremely limited.

Factors that may contribute to, or trigger, central sensitization

The figure shows a simplified schema of factors that may contribute to central sensitization and central sensitivity syndrome.

Simplified suggested biopsychosocial mechanisms for central sensitization and central sensitivity syndromes with interacting factors



Source: Figure 2 of Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):342.

Yunus explains genetic predisposition, the autonomic nervous system, neuroendocrine dysfunction, psychological factors and infection, inflammation, trauma, sleep, and environmental factors[2].

• Genetic predisposition

Pain is generally known to be modulated by genetics. Polymorphisms such as T102C polymorphism (5-HT2A receptor) and serotonin-transporter gene polymorphism have been reported in fibromyalgia, irritable bowel syndrome, temporomandibular disorder, migraine, chronic fatigue syndrome, and depression.

• Autonomic nervous system

Spectral analysis of heart rate variability has revealed overactivity of the sympathetic nerves and underactivity of the parasympathetic nerves in disorders including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and restless legs syndrome.

• Neuroendocrine dysfunction

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction with hypocortisolism is common to many forms of central sensitivity syndromes (fibromyalgia, chronic fatigue syndrome, chronic headache, and post-traumatic stress disorder). The relationship between low cortisol and central sensitization is still unclear, but a stress mechanism may be involved.

• Psychological factors

Anxiety, stress, depression, and other psychological problems are common in central sensitivity syndromes, and studies have shown that their relationship may be bidirectional. However, data are sparse regarding the association between psychological distress and central sensitization. Adverse experiences in childhood may promote long-term neuroplasticity, causing mental and physical symptoms similar to those of central sensitization in adults.

• Infection, inflammation, trauma, sleep, and environmental factors

General or local viral infections, as well as trauma, are reported to trigger central sensitivity syndrome symptoms through the action of inflammatory mediators that activate nociceptive fibers with resultant central sensitization.

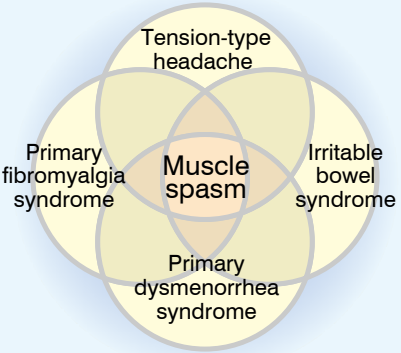
Non-restorative sleep may also cause central sensitization. Central sensitization as measured by algometry and nociceptive stimuli are also associated with poor sleep. Environmental stimuli such as noise may also induce central sensitization.

② Historical development of the concept of central sensitivity syndromes

Yunus has summarized the history of his concept of central sensitivity syndromes in the table below.

Yunus is a doctor and researcher who specializes in fibromyalgia. While treating fibromyalgia patients, he noticed commonalities among four diseases and syndromes (primary fibromyalgia syndrome, tension-type headache, primary dysmenorrhea syndrome, and irritable bowel syndrome), and first expressed these in the form of a Venn diagram in 1984. At that point, the common mechanism for these four conditions was unclear, and almost nothing was known about central sensitization. He therefore depicted the common factor as "muscle spasm," the idea of which had been popularized by the Mayo Clinic. The initial diagram was received with suspicion [1 4]. It may be presumed that Yunus' concept was not accepted without resistance by the medical community from the fact that two of the publications listed in the table were an abstract and a supplement rather than easily obtainable, well-known journal articles.

The first proposed concept of overlapping syndromes shown in a Venn diagram in 1984



Source: Figure 2 in Yunus MB. Central sensitivity syndrome: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008 Jun;37(6):345.

History of central sensitivity syndromes

1981	First data-based demonstration of associations among fibromyalgia syndrome and tension-type headache, migraine, and irritable bowel syndrome.	Yunus MB, *et al*. Primary fibromyalgia (fibrosotis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981;11:151–71.
1984	First conceptual depiction (by a Venn diagram) of an interrelationship among several central sensitivity syndrome members with similar and overlapping features. Muscle spasm theorized to be the common pathophysiologic link.	Yunus MB. Primary fibromyalgia syndrome: current concepts. Compr Ther. 1984 Aug;10(8):21–8.
1985	Use of the terminology "stress-related syndromes".	Yunus MB, Masi AT. Association of primary fibromyalgia syndrome with stress-related syndromes. Clin Res 1985;33(4)(Abst):923a.
1989	"Affective" mechanism is suggested for fibromyalgia syndrome and overlapping syndromes, including several medical ("functional") as well as the psychiatric condition described as "affective spectrum disorder".	Hudson JI, Pope HG Jf. Fibromyalgia and psychopathology: is fibromyalgia a form of "affective spectrum disorder"? J Rheumato Suppl 1989;19:15–22.
1994	The collective term "dysfunctional spectrum syndrome" is suggested implying the dysfunction of the neurohormonal system as the common binding mechanism among the central sensitivity syndrome members.	Yunus MB Psychological aspects of fibromyalgia syndrome: a component of the dysfunctional spectrum syndrome. aillieres Clin Rheumatol. 1994;8(4):811–37.
2000	The nosology "central sensitivity syndromes" is coined based on the evidence that fibromyalgia syndrome and overlapping members of the central sensitivity syndromes family demonstrate central sensitization to multiple stimuli. Central sensitization is proposed to be the common pathophysiological binder of the central sensitivity syndrome diseases.	Yunus MB. Central sensitivity syndromes: a unified concept for fibromyalgia and other similar maladies. Journal of Indian Rheumatism Association. 2000 Mar;8(1):27–33.

Adapted from Table 1 in Yunus MB. Central sensitivity syndrome: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum. 2008 Jun;37(6):346.

③ From fibromyalgia to central sensitivity syndromes: Clinical significance

Yunus' worldview and the clinical significance of central sensitivity syndromes

Finally, I will explain the background to how Yunus came to coin the term "central sensitivity syndrome" despite being a fibromalgia researcher, and his emphasis on its clinical significance. This was based on his own worldview, which rejects the dualisms (see note) prevalent in medical science of mind versus body and disease versus illness, and emphasizes the importance of the biopsychosocial approach and patients' subjective complaints of pain in clinical practice as a whole, not just the treatment of central sensitivity syndromes [5]. Yunus supports Engel's 1977 "biopsychosocial" concept and terminology, and in addition to explaining the mechanism of pathophysiologic central sensitization as the common factor in disorders classified as central sensitivity syndromes, he also emphasizes the importance of biopsychosocial factors in their treatment. He poses the question to the medical establishment of the fundamental nature of "treatment" devised in collaboration with real-life patients by combining effective drug therapies with other types of treatment, as opposed to the idea that standard, guideline-based treatment is the gold standard.

In view of these points, the concept of central sensitivity syndrome championed by Yunus is clinically significant for two major reasons. The first is that elucidating the mechanism common to central sensitivity syndromes would make it possible to avoid the enormous drug development costs and time required for clinical trials for different conditions as well as to alleviate patients' sufferings earlier by using drugs that will clearly be effective on theoretical grounds [2]. The other is that providing a pathophysiological explanation rather than just dismissing patients' pain and unhappiness as nothing but "mental problems" helps to maintain good doctor-patient relationships and enables doctors to provide more satisfactory medical care [1].

Studies of the pathophysiological mechanisms of central sensitivity syndrome disorders are expected to make further advances while incorporating gene analysis techniques. On the other hand, it should not be forgotten that choices

of treatment that have a theoretically solid explanation should not be excluded, even if they cannot all be "scientifically" explained. Yunus' concept of central sensitivity syndromes will undoubtedly undergo further development in the future, but this is where its historical significance lies at this point.

(Note) Dualism: Here, this refers to the mind-body dualism propagated by the 17th-century philosopher Descartes, in which the mind (spirit or soul, ego or psyche, consciousness) exists separately from the things of this world (corporeal or physical).

④ My own concept of "cephalic hypersensitivity syndrome" and Yunus' central sensitivity syndromes

Toshihiko Shimizu may have been the first person to use the Japanese phrase "*nō kabin syōkōgun*" to refer to headaches developed from migraine. This concept partially overlaps my concept of cephalic hypersensitivity syndrome; however, it mainly focuses on headache. Unfortunately, Shimizu did not write about the mechanism of the syndrome, omitted scientific discussions, and presented only a small number of clinical cases [6]. To the best of my knowledge, Yunus originally demonstrated a spectrum of diseases common to central sensitivity or hypersensitivity. Therefore, here I will describe my own theoretical concept of cephalic hypersensitivity syndrome in comparison with Yunus' central sensitivity syndromes.

Definitions of the terminology used in my theory

Cephalic hypersensitivity syndrome

The series of symptoms caused by hypersensitivity of the brain are the result of the synaptic plasticity and functions for the maintenance (or adaptation) of homeostasis that are built in to all animals. Symptoms such as headache, stiff shoulders, lower back pain, fatigue, and misery are induced by chronic physical or mental stress or the overuse of medication, which disturb the autonomic nerves or brain hormone homeostasis and are transformed into various manifestations of chronic pain.

Synaptic plasticity

This refers to the plasticity of the efficiency of neurotransmission across

synaptic connections as a result of the increase or decrease in synaptic connections due to sensory, emotional, and intellectual stimuli. This plasticity contributes to long-term potentiation (LTP) or long-term depression (LTD) in neurons. Neurotransmission efficiency varies according to nerve activity in accordance with what stimuli have been experienced.

Homeostasis maintenance (or adaptation) functions

The integrated biological regulatory system that comprises the nervous system, immune system, and endocrine systems is the foundation of the mechanisms for the maintenance of homeostasis. Synaptic plasticity does not stop at neuronal plasticity, but is intimately related to changes in the immune and endocrine systems, and this transformation is remembered as alterations in the expression of neuronal genes in the cerebral limbic system (the hippocampus and amygdala) and the hypothalamic-pituitary-adrenal (HPA) axis to develop a new "system." Alterations in this system are passed down from the mother to the next generation. The plasticity of the entire system thus involves a genetic component and varies by age and sex. Adaptation includes both individual and evolutionary adaptations.

Chronic illness syndromes and pain

Chronic illness syndromes are manifestations of "pain," and suggest the type of noxious/nociceptive stimulus. Nociceptive stimuli include input from the sensory organs or periphery (exogenous stimuli) and input generated by emotion or thinking (endogenous stimuli).

My theory is a concept that overlaps with that of Yunus in many ways, but differs on the following points. Yunus emphasizes the commonalities among a group of disorders, but this approach includes numerous subgroups, such as patients who do not meet the fibromyalgia guidelines but who nevertheless complain of similar symptoms. With regard to this issue, Mary-Ann Fitzcharles and Yunus have stated that they treat even patients who do not meet the diagnostic criteria for fibromyalgia listed in the guidelines as fibromyalgia patients, emphasizing not only the objective criteria set out in the guidelines but also the patient's own subjective complaints [5]. My hypothesis, on the other hand, emphasizes the patients' subjective complaints, and for phenomena classified as "chronic illness syndrome" with no objective signs such as test results, I infer the source of

nociceptive stimuli on the basis of careful medical interviews with these patients.

Yunus has defined central sensitization as the common mechanism underlying central sensitivity syndromes, and as described earlier, has set out factors that contribute to or trigger central sensitization. My hypothesis regards such psychosocial factors as exogenous or endogenous stimuli providing inputs, and explains it as the transformation by these inputs of the integrated biological regulatory system and individual and evolutionary adaptation. It can easily be conjectured that symptoms will thus vary by sex and age, and the effect of the environment surrounding an individual can also be readily inferred, enabling the appropriate treatment for each individual patient to be selected.

2 Hypothesis 2: Cephalic hypersensitivity syndrome can be explained in terms of the molecular biology of synaptic plasticity

Treatment for cephalic hypersensitivity syndrome has the goal of alleviating the pain of which the patient complains. Methods other than drug treatment are also important, such as the improvements in lifestyle and thinking described in Chapters 1 and 2, but it is important to identify the appropriate type of drug, dosage, and method of administration for each individual patient. Basic to this are the molecular biology of synaptic plasticity and pharmacological inferences. Many patients with cephalic hypersensitivity syndrome have long suffered from a range of forms of pain of unknown origin, and may also be suffering from symptoms that have undergone complex alterations as a result of the overuse of symptomatic painkillers or the wrong choice of medication. My hypothesis concerning synaptic plasticity disentangles such episodes of transformed pain, and is useful for increasing the chance of selecting appropriate medication.

In my encounters with patients with cephalic hypersensitivity syndrome, many patients have said that their motivation for coming to me was that they had visited several other hospitals and tried a variety of different medications, but their symptoms had worsened rather than improved. I have often also heard that they hadn't believed that medication at such low doses would be effective, and that although they had been surprised to find out that they were being prescribed antiepileptics, their symptoms had greatly improved (see Part 2). What this suggests is just how difficult it is to select the right type of drug and dosage. What first led me to the discovery of the concept of cephalic hypersensitivity syndrome was the fact that low doses of antiepileptics and antidepressants were effective treatments for a range of different chronic illness syndromes. These are drugs that act on excitation of the cranial nerves. Despite the fact that over the past 40 years, the molecular biology of the cranial nervous system has advanced rapidly, including gene analysis techniques, many aspects still remain unclear. Elucidation of their mechanisms is a task for the future, but here I shall describe current knowledge that backs up my hypothesis (although this is not a scientific review) and explain the thinking underlying my algorithm of treatment.

My inferences concerning ion channels and brain hormones

Ion channels are the basis of all cellular activity. This means that there are also several mechanisms for maintaining homeostasis in neurons. I have arrived at the following inferences on the basis of the shared pharmacological characteristics of the drugs I use to treat patients with cephalic hypersensitivity syndrome.

① Membrane potential-dependent ion channels may predominate in exogenous pain caused by stimuli such as touch and temperature, whereas ligand-dependent ion channels may predominate in endogenous pain such as emotional and intellectual pain.
② Some ion channels are believed to be associated with time-dependent brain hormones. This is evidence that night therapy may be effective for cephalic hypersensitivity syndrome.
③ Long-term potentiation of pain-related neurons involves a channel function system in which calcium ion inflow is predominant, and magnesium ions may be important in suppressing this system.

The choice of the easiest medication for individuals to take: Finnerup *et al.*'s work

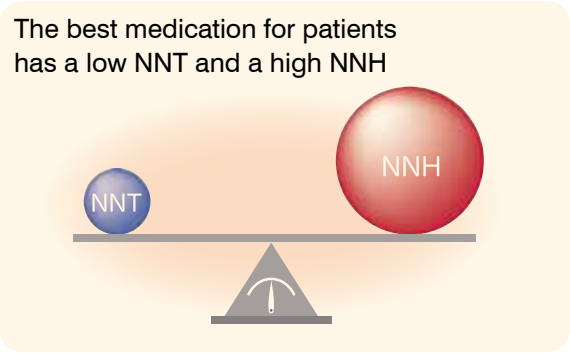
I have already discussed the significance of Yunus' proposed central sensitivity syndrome above. One thing that central sensitivity syndrome and my own proposed cephalic hypersensitivity syndrome have in common is that they are both disease concepts born out of our experience of clinical treatment with the goal of providing treatment that is easy for people to undergo. The work of Finnerup and her colleagues is extremely relevant as an effective approach to the selection of medication that makes it easy for people to undergo treatment[7,8]. Finnerup works in the Department of Neurology and the Danish Pain Research Center of Aarhus University Hospital, and uses pharmacoepidemiological techniques to investigate the balance between the effectiveness of various types of painkillers and their side effects, as well as the cost-benefit performance of development costs.

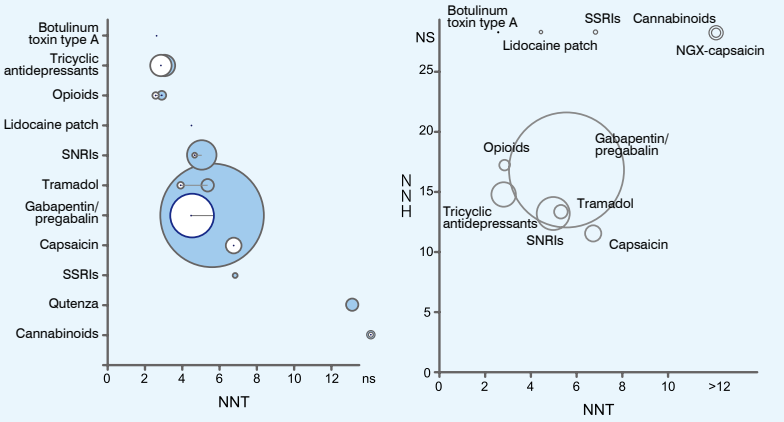
This is also an issue in Japan; the close relationships between doctors and pharmaceutical companies in clinical trials for drug development and the intensification of competition in drug development in many countries mean that

the basic nature of treatment is being overlooked. Despite the fact that the goal is the standardization of evidence-based treatment, drug development is at root carried out under political and economic pressure, far from the best principle for patients, who want low-cost drugs that are effective in low doses. As I mentioned earlier, Yunus has also raised this issue [2]. Finnerup and her colleagues analyzed painkillers, and as there is a large overlap between the drugs mentioned in their work and those used to treat cephalic hypersensitivity syndrome, their results are a useful reference from the viewpoint of drug selection, and I shall describe some of them here.

Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

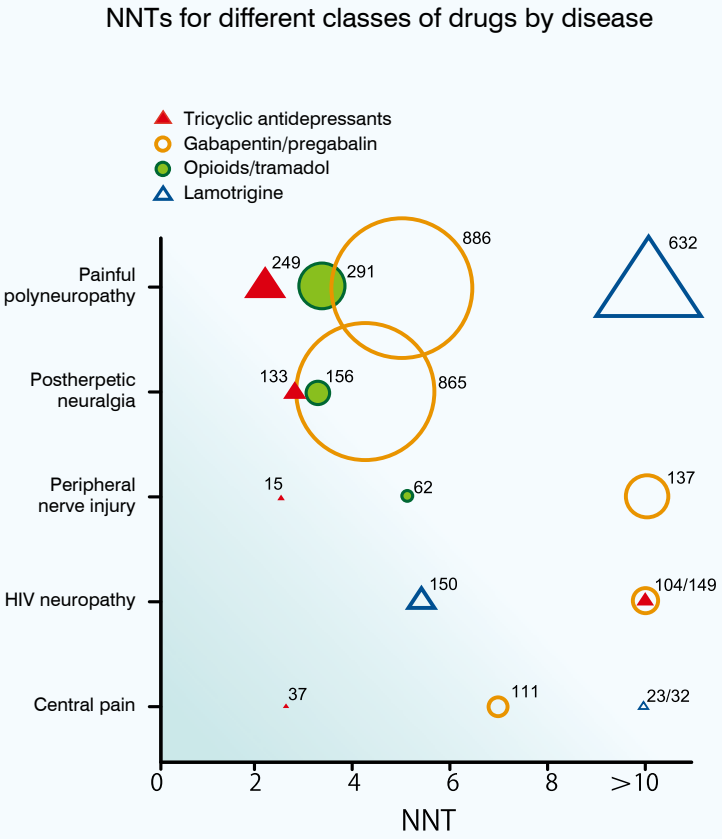
The number needed to treat (NNT) is an index of how many patients must be treated in order to achieve the effective treatment of a single case, and the number needed to harm (NNH) is an index of how many patients will be treated for an adverse event (side effect) to appear in a single case [9]. Generally speaking, if two medications have very similar mechanisms of action, the one with the lower NNT and higher NNH is chosen, as this is the best choice for the patient. The use of the NNT for evaluation has been criticized, but as an index for comparing studies carried out using different designs, it is a significant resource for deciding on which medication to use in clinical settings [7].





NNT and NNH for central and peripheral neuropathic pain, excluding trigeminal neuralgia
Left: The white circles show data from 2005, and the blue circles from 2010. The circle sizes indicate the relative number of patients who received active treatment drugs.
Right: 2010 data on the NNT and NNH for each class of drug. The placebo effect varied depending on the study design.
The circle sizes indicate the number of patients who received active treatment drugs.
Adapted from Figure 1.3 in Finnerup. NB., Sindrup. SH. & Jensen. TS. The evidence for pharmacological treatment of neuropathic Pain. 2010 Sep;150(3), 573-81.
Figure caption was omitted.

Reading the top figure from left to right, gabapentin and pregabalin are administered to large numbers of patients compared with other medications of almost the same pharmacological effectiveness. This tendency is particularly pronounced in comparison with tricyclic antidepressants (TCAs) and serotonin-noradrenaline reuptake inhibitors (SNRIs). The next figure shows that gabapentin and pregabalin have been the subjects of large-scale studies of polyneuropathy and postherpetic neuralgia, both of which cause severe pain, and that although they have also been shown to be effective against peripheral neuropathy and central pain, those were small-scale studies.



The symbol sizes indicate the relative number of patients who received active treatment drugs. Adapted from Figure 2 in Finnerup. NB., Sindrup. SH. & Jensen. TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 150, (2010), 573-81.
Figure caption was omitted.

Both Finnerup and Yunus hold that the massive research costs involved in repeating a new clinical trial for every different disorder are reflected in drug prices and medical costs, and this is therefore not in the patient's best interest. There is a need to consider expanding the indications for effective drugs for diseases that have the same underlying mechanism, a process that does not necessarily require clinical trials that entail large amounts of money and time. It may also be possible to use the scientific and theoretical evidence obtained from the close observation of patients on an everyday basis and analysis, an attitude that is also common to the way of thinking that is key to the treatment I provide.

Medications for treating cephalic hypersensitivity syndrome and the molecular biology of synaptic plasticity

At the risk of repeating myself yet again, patients with cephalic hypersensitivity syndrome have a wide variety of complaints. I have inferred the mechanisms of these disorders from the commonalities of the drugs that treat them effectively. The table compares the medications for treating cephalic hypersensitivity syndrome described in Chapter 1 with the recommendations given in the guidelines for epilepsy, depression, chronic headache, fibromyalgia, and chronic pain, and summarizes their mechanisms of action. The table given as a reference was presented as the clinical pharmacological characteristics of antiepileptics, and what can be seen from these two tables is that many antiepileptics have an inhibitory effect on sodium and calcium ion channels.

Column

●The wisdom of older people

I have already mentioned Gerson therapy, the main pillar of which is a low-salt diet, in Chapter 1, but while reading Gerson's works, I suddenly remembered something. This was about pine trees. When I was a boy, my grandmother used to put bundles of pine needles tied up with string into the bath. "You should really use needles from pine trees that grow by the sea, but you can't get those here," she would say. Some decades later, I was making a business visit to Gengo Tsujita, Director of the Tuberculosis Sanitorium (the present-day Minami-Okayama Medical Center), when I noticed that the sanitorium was set within a dense pine wood. It offered its patients the benefits of a pine "forest bath."

The wisdom of our elders is a mighty thing, and this is not limited to pine trees. Today, a type of polyphenol extracted from pine needles and other sources is the focus of attention as being effective against menopausal syndrome and a range of lifestyle-related diseases, and research into its anticancer properties is also underway.

Yunus and Gerson were both clinicians as well as researchers. Since leaving the research laboratory at Okayama University, I too have been dealing with sick people to the best of my ability as a regular doctor. What I have felt over my long experience in everyday clinical practice is the universality of that phenomenon known as "sickness," and the wisdom of those people who have been faced with it. Drugs are useful, but most of them have been synthesized from natural medicinal plants or substances obtained as a result of our ancestors' experience. Substances that exist in the natural world will be easiest for people to use if they are taken in a form and at a dose close to their natural state. Yunus, Gerson, and I share similar ideas on this point.

I believe that a doctor's prescriptions and treatment policies should be based on a way of thinking that incorporates this viewpoint.

Overlap between medication for the treatment of cephalic hypersensitivity syndrome and drugs recommended in treatment guidelines, and their mechanisms of action

First-choice medication for cephalic hypersensitivity syndrome (Oota)	Guideline recommendations					Potential-dependent Na-channel blocking	Inhibitory neural potentiation by GABA concentration/function enhancement	Glutamate liberation, receptor blocking	Anion transfer blocking by carbonic anhydrase inhibitor in the brain	Membrane potential-dependent Ca-channel blocking	Reduced neurotransmitter release by synaptic vesicle protein binding	Blocking of serotonin/noradrenaline reuptake in the brain	Blocking of serotonin/dopamine reuptake in the brain
	① Epilepsy	② Depression	③ Chronic headache	④ Fibromyalgia	⑤ Chronic pain								
Tryptanol (amitriptyline)/Noritren (nortriptyline)		●	●	●	●							○	
Depakene (sodium valproate)	●	●	●				○	○					
Rivotril (clonazepam)	●		●			○	○						
Risperdal (risperidone)													○
Tegretol (carbamazepine)	●	●	●		●	○							
Lamictal (lamotrigine)	●	●	●			○		○		○			
Topina (topiramate)	●		●			○	○	○	○	○			
E Keppra (levetiracetam)	●				●						○		
Mystan (clobazam)	●					○	○						
Gabapen (gabapentin)	●		●	●	●		○			○			

① Japanese Society of Neurology (Editorial supervisor): Clinical Guidelines for Epilepsy Management 2010. Igaku Shoin. [In Japanese]
② Japanese Society of Mood Disorders Treatment Guidelines 2012. [In Japanese]
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④ Japan College of Fibromyalgia Investigation (Editor): Fibromyalgia Guidelines 2013. Japan Medical Journal 2013. [In Japanese]
⑤ Japanese Society of Neurological Therapeutics (Editorial Supervisor): Standard Neurological Therapy: Chronic pain 2013. [In Japanese]

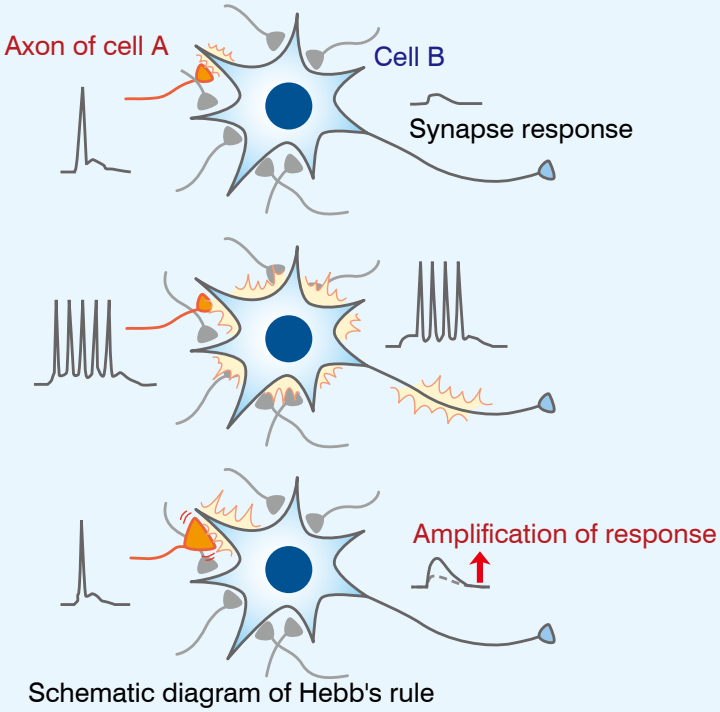
Reference: Clinical pharmacological characteristics of antiepileptics

Generic name	Mechanism of action	Indications	Normal dose		Biological half-life (hours)	Time to reach peak value (hours)	Time to reach steady-state (days)	Protein binding rate (%)	Therapeutic serum concentration range (μg/ml)	Main side effects
			Adult (mg/day)	Child (mg/kg/day)						
Phenobarbital (PB)	Ca, GABA, Glu, etc.	Ps, s-GTC, GTC	50~150	2~5	20~130	1~5	14~21	45~60	10~25	Sedation, drowsiness, disquiet, agitation, hyperactivity, rash, abnormal bone metabolism, low folic acid
Primidone (PRM)	Na, PB mechanisms	Ps, s-GTC, GTC	250~1,000	10~20	3~16	2~4	4~7	0~22	4~12	Sedation, drowsiness, weakness, ataxia, hyperactivity, double vision, dizziness / vertigo, rash
Phenytoin (PHT)	Na, Ca, etc.	Ps, s-GTC, GTC	100~300	3~10	7~42	2~12	4~10	80~95	10~20	Nystagmus, double vision, ataxia, gingival proliferation, hirsutism, rash, liver damage, immunosuppression, low folic acid, megaloblastic anemia
Carbamazepine (CBZ)	Na, Glu, etc.	Ps, s-GTC, GTC	200~1,200	5~20	3~26	2~8	3~7	65~85	3~12	Dizziness / vertigo, double vision, nystagmus, ataxia, drowsiness, rash, gastrointestinal disturbance, leukopenia, decreased folic acid, hyponatremia, liver damage
Zonisamide	Na, Ca, GABA, Glu, etc.	Ps, s-GTC, GTC, My; WS, LGS	200~600	4~10	24~60	2~6	10~15	45~50	10~30	Drowsiness, enervation, slowing of mental activity, loss of appetite, hypohidrosis, kidney/urinary tract stones
Sulthiame (ST)	Carbonic anhydrase inhibitor	Ps, s-GTC, GTC	200~1,000	5~10	2~10	1~5	-	-	6~20	Heavy-headedness, hyperventilation, loss of appetite, paresthesia, ataxia, drowsiness
Gabapentin (GBP)	Na, Ca, GABA, Glu	Ps, s-GTC, GTC	900~1,800	30~40	4~7	2~3	2	0~3	2~20	Drowsiness, dizziness / vertigo, headache, double vision, malaise, aggravated seizures, emotional instability, abnormal behavior
Topiramate (TPM)	Na, Ca, GABA, Glu, Carbonic anhydrase inhibitor	Ps, s-GTC, GTC, My, Ab; LGS	200~400	1~9	12~30	1~4	3~5	13~17	9~12	Drowsiness, dizziness / vertigo, decline in cognitive function, weight loss, kidney/urinary tract stones, metabolic acidosis, hypohidrosis
Acetazolamide (AZA)	Carbonic anhydrase inhibitor	Ab, My, GTC, s-GTC, Ps; WS, LGS	200~750	10~20	10~15	1~3	2~5	90~95	8~20	Dizziness / vertigo, paresthesia, headache, loss of appetite, polyuria, dry mouth, weakness
Ethosuximide	Ca	Ab, My	500~1,500	10~30	25~60	1~4	6~12	0~10	40~100	Gastrointestinal disturbance, drowsiness, abnormal behavior, hiccups, bone marrow suppression, rash, generalized erythematosus
Valproate sodium (VPA)	Na, Ca, GABA, Glu, etc.	Ab, My, GTC, s-GTC, Ps; WS, LGS	500~2,000	10~30	4~15	0.5~4 4~10 (sustained-release formulation)	2~4	84~95	40~100	Gastrointestinal disturbance, liver damage, coagulation disorder (low platelet count/fibrinogen), obesity, hair loss, diuresis, tremors, drowsiness, pancreatitis
Diazepam (DZP)	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	4~30	0.2~0.7	8~40	1~3	3~10	96~98	0.2~0.5	Sedation, drowsiness, decline in mental activity, ataxia, low muscle tone, salivation, excessive airway secretions
Nitrazepam	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	2~20	0.1~0.5	18~35	1~4	6~8	85~88	0.02~0.2	Sedation, drowsiness, decline in mental activity, ataxia, low muscle tone, salivation, excessive airway secretions
Clonazepam (CZP)	Na, Ca, GABA	Ab, My, GTC, s-GTC, Ps; WS, LGS	1~10	0.05~0.2	20~40	1~4	4~6	86	0.02~0.08	Drowsiness, decline in mental activity, ataxia, low muscle tone, abnormal behavior, sleep disturbance, salivation, excessive airway secretions
Clobazam (CLB)	Na, Ca, GABA, etc.	Ab, My, GTC, s-GTC, Ps; WS, LGS	10~30	0.2~0.8	10~30	1~4	6	83~85	0.1~0.4	Drowsiness, decline in mental activity, ataxia, low muscle tone, abnormal behavior, sleep disturbance, salivation, excessive airway secretions

Na: Na^+ channel inhibition; Ca: Ca^{2+} channel inhibition; GABA: γ-aminobutyric acid (GABA) activation; Glu: glutamate suppression; Ps: partial seizures; s-GS: secondary generalized seizures; GTC: generalized tonic-clonic seizures; Ab: absence seizures; My: myoclonic seizures; Ws: West syndrome; LGS: Lennox-Gastaut syndrome.
Source: Table 1 in Yamatogi, Yasuko. Drug treatment of childhood epilepsy. Journal of the Japanese Medical Association 136(6), P.i090. [In Japanese]

• **Synaptic plasticity**

Hebb's rule is a hypothesis postulated by Canadian psychologist Donald Hebb in 1949, which predicted that if the firing of neuron A results in the firing of neuron B, the connection between those two neurons will strengthen. This is the basic phenomenon in the brain that underlies learning. Today, the rule of synaptic plasticity proposed by Hebb, based on the theory that long-term changes at a synapse (the junction between two neurons) change the efficiency with which signals are transmitted, constitute the mechanism of learning, is known as Hebb's rule [10].



Schematic diagram of Hebb's rule

It has already been suggested that the mechanism of long-term potentiation in synaptic plasticity may be involved in the development of allodynia and hypersensitivity through somatosensory stimulation [11–14]. Many of the drugs on which I have focused as effective treatments for cephalic hypersensitivity syndrome, such as antiepileptics and antidepressants, act to block sodium and calcium channels. Work is still in progress on the molecular biological analysis of ion channels, including genetic factors, and the construction of a model that explains the entire picture may well not be a simple matter. Classically, cells possess ion channels, and the major principle that if their functions are not preserved then life cannot be maintained is true for every type of disease. The human body has developed systems for maintaining homeostasis that appear complex and elaborate at first glance, but the majority of the elements that compose amino acids, as well as the ions that are released and received at the synaptic terminals, belong to a limited range that are common on Earth: nitrogen, carbon, oxygen, hydrogen, calcium, magnesium, phosphorus, sodium, potassium, and a few others. When eukaryotic organisms first emerged around 2.2 billion years ago, the main elements available for them to use were potassium and magnesium. During the long process of evolution, cells came to store potassium and magnesium inside themselves while as far as possible excreting elements that subsequently became more common in the planetary environment, such as sodium and calcium, outside the cell, and these thus came to be used as the signals forming the intercellular network.

In this light, it is natural to focus on the metabolic functions and kinetics of Na^+, K^+, Ca^{2+}, Mg^{2+}, and other elements that account for the majority of ions, as well as amino acids, amines, and other neurotransmitters, when looking at the underlying mechanism of cephalic hypersensitivity syndrome. So far, the following discoveries have been made that may contribute to a molecular biological explanation of cephalic hypersensitivity syndrome.

- Among the neuronal Na^+ channel subunits, those associated with pain are Nav 1.3, Nav 1.7, and Nav 1.8, but currently there is no medication that acts specifically on those subunits [15–18].
- Nociceptive stimuli, including pain sensation, are transmitted via Type A δ and Type C fibers, with Type C being the main type associated with hyperalgesia.

High-voltage-activated calcium channels are involved in the occurrence of hyperalgesia and allodynia. Type A β fibers are also involved in allodynia [19].

- Long-term potentiation of pain-related neurons and synaptic plasticity are caused by calcium ion influx through NMDA receptors. NMDA receptor activation is blocked by magnesium ions at normal membrane resting potential, but if input by repeated impulses leads to the maintenance of depolarization by AMPA receptors and others, electrical repulsion causes the magnesium to dissociate, activating the NMDA receptors [20].
- When NMDA receptors are activated by depolarization, the calcium ion influx elevates the intracellular calcium ion concentration, activating Ca^{2+}/calmodulin-dependent protein kinase, protein kinase C, and the tyrosine kinase Fyn, inducing long-term potentiation [20].
- The magnesium ion blocking of NMDA receptors is essential for the induction of the expression of genes associated with long-term memory [21].
- The monoamine hypothesis: Monoamines are a class of neurotransmitters that include dopamine, noradrenaline, adrenaline, serotonin, and histamine. Hypotheses have been proposed for the involvement of the noradrenaline, serotonin, and dopamine systems in depression; the centrality of the dopamine system in bipolar disorder, with the additional involvement of noradrenaline and serotonin; the involvement of the serotonin system in anxiety disorder; and the centrality of the dopamine system in schizophrenia, with the additional involvement of NMDA-type glutamate receptors [22].
- The nervous system, immune system, and endocrine system are engaged in integrated biological regulation as an interacting complex system while maintaining the individual systems [23 24].

Nervous system–endocrine system: hypothalamic hormones–anterior pituitary hormones

Anterior pituitary-releasing hormones: growth hormone-releasing hormone, growth hormone-inhibiting hormone, prolactin-inhibiting hormone, thyrotropin-releasing hormone, corticotropin-releasing hormone, gonadotropin-releasing hormone

Posterior pituitary hormones: vasopressin, oxytocin

Nervous system–(endocrine system)–immune system: Hypothalamic–pituitary–adrenal system → immune system

Hypothalamic–pituitary–gonadal system → immune system
Hypothalamic–pituitary–thyroid system → immune system
Sympathetic nervous system–noradrenaline → immune system
Parasympathetic nervous system–substance P, dopamine, calcitonin gene-related peptide, corticotropin-releasing hormone, gonadotropin-releasing hormone → immune system
Vagus nerve–acetylcholine → immune system

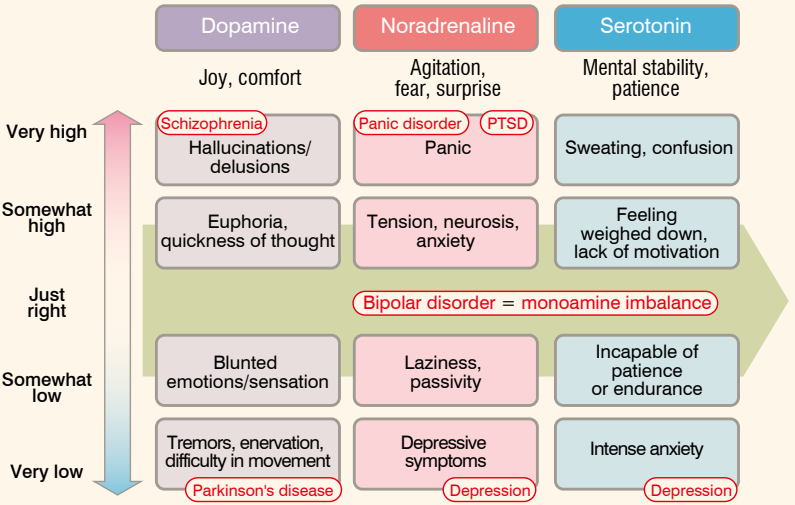
Vagus nerve → interleukin 1, interleukin 6, tumor necrosis factor α ← (inhibition) interleukin 4, interleukin 10, transforming growth factor β
Glial cells[25]/microglia, astrocytes, oligodendrocytes, etc. → immune system

From brain neurohormones to cephalic hypersensitivity syndrome: Commonalities with psychiatric and neurological disorders

I believe that it is the serotonin and dopamine systems that are generally involved with cephalic hypersensitivity syndrome. It may be that easily treated cases of cephalic hypersensitivity syndrome involve the serotonin system, whereas less easily treated, so-called intractable cephalic hypersensitivity syndrome, involves the dopamine system.

As I explained in Chapter 1, brain hormones comprise dopamine, noradrenaline, adrenaline, and acetylcholine, which work smoothly together thanks to serotonin, which plays a motherly role. Cephalic hypersensitivity syndrome does not develop if these hormones are in balance. What opens the door to cephalic hypersensitivity syndrome is not a potentially life-threatening major injury or illness, but rather the accumulation of everyday stress. Stiff shoulders and fatigue are the most obvious signs. The illustration shows the relationship between psychiatric and neurological disorders and an excess or deficiency of the three neurotransmitters apart from acetylcholine. Of course, in all cases, the real story is too complicated to be explained by a single substance, but depression is linked to the serotonin system, whereas schizophrenia and Parkinson's disease are linked to the dopamine system. Compared with schizophrenia, depression is

more strongly influenced by environmental than genetic factors and has a high rate of complete recovery if no other psychiatric disorders are present. Although the therapeutic environment for schizophrenia is far better today than it once was, it is more complex than depression, and complete recovery is difficult. In terms of its long-term prognosis, it will become severe in 10–20% of people, who will not recover [26]. New treatments are also being tried out for Parkinson's disease, which is a designated intractable disease. The same factors apply as with cephalic hypersensitivity syndrome. The latter can be better understood if it is broadly divided according to the serotonin system + noradrenaline system and the dopamine system. The serotonin type is characterized by depression, anxiety and tension, and hypersensitivity, and I earlier explained it in terms of



Monoamine neurotransmitters regulate emotions such as joy, fear, and anxiety and play a central role in the memory of emotions, and abnormalities in their metabolism or signal transmission are closely related to psychiatric symptoms and disorders.

Monoamine excess or deficiency and psychiatric and neurological disorders (Source: Report of the Brain Symposium in Nagoya 2013) [In Japanese]

the mechanism of the autonomic nerves, which are also the part of the nervous system that becomes hypersensitive to pain stimuli. Many patients with cephalic hypersensitivity syndrome who complain of headache and other pains or stiff shoulders are thus of the serotonin type. It is usually easy to build up a good doctor-patient relationship with this type, and as they also make an effort to follow the treatment plan, they recover comparatively more readily.

Patients with the dopamine type, on the other hand, do not complain of pain despite their entire body being stiff and tight, perhaps because they have become dulled to feeling pain.

I have the impression that the more a patient talks loquaciously about their own complaints, the less likely they are to be meekly persuaded by the doctor's explanation, and little can be expected of them in terms of cooperating with the treatment plan.

What action do these neurotransmitters exert on our "minds," and how can the relationship between the stress of interpersonal relationships caused by the activity of the "mind" and the development of an illness be explained in terms of molecular biology? Both of these questions have yet to be properly answered.

Acetylcholine, the key player in cephalic hypersensitivity syndrome: from chronic mental pain to chronic physical pain

Chronic pain that is purely physical does not lead to the development of cephalic hypersensitivity syndrome. It is mental chronic pain that opens the door. As I have mentioned before, a molecular biological hypothesis has been proposed in which depression and schizophrenia are caused by a disturbance in the balance of monoamine brain neurohormones such as serotonin, but I conjecture that a different key player, acetylcholine, is deeply involved in cephalic hypersensitivity syndrome. My hypothesis is that acetylcholine causes chronic physical pain from the chronic mental pain due to the disrupted balance in serotonin and dopamine in the brain via its action on the autonomic nerves, or that it amplifies existing physical pain via chronic mental pain and the autonomic nerves, leading to the development of intractable cephalic hypersensitivity syndrome.

In Parkinson's disease, there is insufficient dopamine and an excess of acetylcholine in the brain. This is manifested as cognitive and motor impairment. In Alzheimer's disease, the level of acetylcholine in the brain decreases, and cognitive impairment occurs. Aricept (donepezil), a drug developed as a treatment for Alzheimer's disease, increases acetylcholine via its cholinergic action and is believed to improve cognitive function. There is now growing evidence that the cause of myasthenia gravis, a disease characterized by diminished muscle strength, is that acetylcholine receptors are one of the target molecules for autoimmunity.

Acetylcholine was identified in the 19th century, and as such is the earliest neurotransmitter to have been discovered. Studies of acetylcholine receptors in the peripheral nerves, and particularly in neuromuscular junctions with muscles innervated by motor nerves, have progressed to the extent of determining their molecular structure [27]. The most important acetylcholine receptors are muscarinic and nicotinic receptors. These have different mechanisms, as muscarinic acetylcholine receptors are G-protein-coupled receptors, and nicotinic acetylcholine receptors are ligand-gated ion channels, but both play important roles in the intracellular and extracellular movement of K^+, Na^+, and Ca^{2+} ions. Acetylcholine has also been shown to enhance the long-term potentiation of memory in the hippocampus [28]. It has been suggested that noradrenaline may also promote this action [29], but many aspects of its joint action and properties together with other brain hormones in the central nervous system remain unclear. The importance of the wide-ranging functions of acetylcholine outside the neurons as a mediator of intercellular communication is gradually being recognized, but has yet to be fully explained. Koichiro Kawashima has stated that acetylcholine is also expressed in plants and eukaryotic organisms that do not possess a nervous system and proposed that it may have been used as a neurotransmitter when animals with a nervous system emerged in the process of animal evolution [30].

In Chapter 1, I explained that cephalic hypersensitivity syndrome is a disease that was predestined when humans acquired the ability to walk on two legs. Acetylcholine has existed on this earth long before the emergence of humanity and has played a role in biogenic activity. Without this premise of these properties of acetylcholine, it is impossible to explain the underlying mechanism of cephalic hypersensitivity syndrome.

In 2013, President Barack Obama of the United States announced the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative providing ten years of priority research funding. Almost simultaneously, Europe and Japan also allocated large amounts of funding to genetic and molecular biological studies of the brain and mind as priority research areas, and these studies are now proceeding.

To explain the mechanism of cephalic hypersensitivity syndrome, it will be necessary to elucidate the relationships between these brain hormones and the nervous system on the one hand and synaptic plasticity and long-term potentiation and depression on the other. This is truly cutting edge. Although a few related studies have been carried out, they are still at the level of animal experiments. Research on cranial neurons, even in other mammals, has in some cases apparently yielded completely contradictory results in animals such as rats and rabbits on the one hand and primates, which form complex social groups, on the other. The American research plan includes the development of neurologically related animal models ranging from nematodes to non-human primates. The brain, described in the Human Brain Project report as consuming "about 30W, the same as an electric light bulb, thousands of times less than a small supercomputer," is becoming better understood, and once studies on the fact that "sickness comes from the spirit," as the Japanese proverb puts it, are explained on the molecular biological level, the majority of my conjectures may well be validated.

3 Hypothesis 3: A biopsychosocial model is appropriate for the treatment of cephalic hypersensitivity syndrome

To repeat myself yet again, Yunus, Finnerup, and I all share a common concern for "treatment that is easy for people to undergo." Yunus in particular has pointed out the importance of the doctor-patient relationship in treatment, and at its root, this is a rejection of the "body–mind" and "disease–illness" dualisms [13]. Yunus frequently uses the term "biopsychosocial" coined in 1977 by George Engel [31] and raises the issue of doctors who make decisions on whether a patient has a "physical disorder" or a "mental disorder" on the basis of objective test results [3 32].

The biopsychosocial model

This model was put forward in 1977 by Engel, who was then Professor of Neurology at Rochester University in the United States. Engel pointed out the limitations of the biomedical model prevalent in the medical establishment by quoting Seymour Kety's 1974 study on the experience of illness by patients with diabetes and schizophrenia, stating that "The presence of the biochemical defect of diabetes or schizophrenia at best defines a necessary but not sufficient condition for the occurrence of the human experience of the disease, the illness. More accurately, the biochemical defect constitutes but one factor among many, the complex interaction of which ultimately may culminate in active disease or manifest illness" [31].

Based on this, he proposed a new medical model in which the way in which illness is experienced by different patients and how this is reported is affected not only by biological factors but also by psychological, social, and cultural ones.

Cognitive behavioral therapy

As I have already described in Chapter 1, Oota-style cognitive behavioral therapy is included in one of the three arrows of my algorithm of treatment, "improving thinking." The cognitive behavioral therapy that now has a firm place in psychotherapy was in its narrow sense systematized by Aaron Beck in the 1960s, and its use along with drug treatment is now recommended in guidelines for the care of conditions including depression, chronic pain, fibromyalgia, and

headache. However, as Beck himself said, cognitive behavioral therapy is at its root a common sense-based approach, and the origins of the idea that people's perceptions are dominant over their feelings and behavior, and that conversely the way in which activities and behavior are carried out can affect thought patterns and feelings, can be traced back to Greek philosophy and Eastern thought. Beck's cognitive behavioral therapy may thus be regarded as a sophisticated methodology, but is not the be-all and end-all.

Cognitive behavioral therapy may be an ancient concept, but clinical studies of its use as a form of psychotherapy are comparatively recent. From the perspective of behavioral therapy, in the 1950s and 1960s, clinicians began to explore the possibilities of desensitization and relaxation training for phobias, based on Pavlov's famous classic conditioning experiments and Skinner's theory of operant conditioning. In terms of emotions and perceptions, Albert Ellis proposed rational emotive behavioral therapy, based on the idea that people make judgments in the light of beliefs rather than events, and that emotions are evoked as a result. It was Beck who first integrated these approaches from various different perspectives and systematized the theory of intervention for emotional disturbance.

Characteristic of the cognitive behavioral therapy developed by Beck is that it is a sophisticated combination of techniques for helping patients to notice their own internal thoughts associated with emotions such as depression, anxiety, and anger, and to correct them themselves. Normally patients undergo between five and 20 sessions lasting 45–50 minutes each. One feature is that it uses the Socratic method to enable patients to recognize and change their non-adaptive thoughts, by asking questions that stimulate their curiosity and intellectual appetite. Other techniques such as psychological education, role play, thought-change journaling, and task-based learning are also used to support patients in changing their own attitudes to rational ones [33].

In my own cognitive behavioral therapy, I do not demand anything difficult. Many of the patients who attend my clinics are already taking multiple medications and suffer from chronic pain and insomnia. Those with personalities that are almost pathologically earnest are not uncommon. They are the sort of

person that if they were told to perform breathing exercises for X minutes Y times a day, they would probably use a stopwatch. What is important is to tell them "It's all right. I'll make everything better," and "Just XX is enough." They have to be healed before they can change their behavior. Elastic band snapping therapy as a way of stopping automatic thinking and Magic Mirror therapy for release from negative thinking and self-affirmation are both effective for this purpose. Naturally these are used in combination with drug therapy.

Randomized comparative studies are in the process of demonstrating that cognitive behavioral therapy has some effect on the psychological aspects of patients with chronic pain or psychosomatic conditions, but studies from the neuroscientific or molecular biological perspectives are only just starting to take shape. As with studies on the mechanisms of pain, there have been a few reports of fMRI and other image analysis studies of changes in areas of the brain that handle emotions, perception, and memory. The day cannot be far off when my own algorithm of treatment, which is now a convincing inference, is accepted in clinical institutions as a matter of course.

Some of the patients who have undergone my treatment have previously been told at other hospitals that they "do not have a disease" and have had the experience of doctors becoming angry with them when they have repeatedly gone to be examined for their complaints. This is exactly the problem with doctors' thinking that was identified by Yunus. The diagnosis of central sensitivity syndromes and cephalic hypersensitivity syndrome is the salvation of patients who have been pigeonholed as suffering from a "frame of mind" or "mental illness" and for whom the wrong treatment has aggravated their symptoms. Its effect is not all a placebo effect, as at its root lies the algorithm of treatment that can be explained in biological, that is, scientific, terms.

At this stage, "standardization" that would enable the diverse range of chronic illness syndromes suffered by patients to be effectively classified and an accurate diagnosis reached has yet to be achieved. Recently, however, it has become possible to use some forms of diagnostic imaging for psychiatric disorders, and this has shown that chronic pain and stress result in atrophy of the hippocampus[14]. The day cannot be long in coming when it will be possible

to diagnose central sensitivity syndromes and cephalic hypersensitivity syndrome by means of an objective index.

Even if an objective diagnosis were to become feasible and treatment could be administered mechanically, however, cognitive behavioral therapy, in which the doctor listens to the patient's complaints about their suffering and enters into a dialogue with their feelings in order to treat them, will become even more important and should not be viewed lightly. It is the doctor's important role to elicit the patient's own biological capacity to heal and to encourage the switch from a vicious cycle to a positive circle of synaptic plasticity. Both Yunus and I are united in this assertion. That means that patients themselves must make an effort and cooperate in the course of their treatment. It is also important to take account of complex influences such as family and work, living environment, and economic circumstances. In this sense, the distortion generated by drug development requiring vast sums of money and the consequent economic competition that was suggested by Finnerup and her colleagues cannot be overlooked.

The table shows a summary comparison of the characteristics of the three of us. Yunus is not arguing about philosophical dualism, but is rather refusing to admit dualistic splits into treatment. I have always held a Buddhist worldview, as will be obvious throughout the cases described in Part 2. No small number of patients have been saved by hearing me speak the words, "I will definitely cure you." Of course, this is a "trick" based on long years of clinical experience. In order to heal and comfort people suffering from illness and pain, treat the innate human capacity honestly, in other words, scientifically. This is my message, and that of Yunus and Finnerup, to the next generation of doctors.

Footnote

Gerson therapy was developed 60 years ago in a very different era, and has therefore not been included in the comparison table. However, Gerson and I do have some things in common in terms of our breadth of vision, looking at the whole of natural science rather than merely medicine, as well as an honest analysis of patients' conditions without limiting the scope of disease. The Gerson therapy that he developed is based on the simple principle of

eliminating cancer cells by normalizing cells and the cellular environment. Although many aspects still remain unclear, this is also consistent with the assertion made by Mina Bissell of the Lawrence Berkeley National Laboratory that if in the right microenvironment, cancer cells are unable to proliferate and will normalize [34]. Gerson never spoke of the difficult position in which he was placed, but according to the biographies written by his daughter and grandchild, he was placed under unjustified pressure by colleagues who were jealous of his unending line of patients as well as by the American medical establishment. Although he never spoke in detail about his own worldview, he was praised by Albert Schweitzer as a true scientist "worthy of the Nobel Prize."

Characteristics of the thinking of Yunus, Finnerup, and Oota

	YunusF	innerupO	ota
WorldviewR	ejects dualism	Not mentioned	Buddhist worldview (non-dualistic)
Specialist field	Rheumatism, fibromyalgia	Neuropathic pain, traumatic neuropathy	Neurosurgery, epilepsy
Claims	Central sensitivity syndrome Developed disease classification and treatment method	Evidence-based pain treatment	Proposed cephalic hypersensitivity syndrome and developed treatment method
Treatment method	Combination of drug therapy and other treatments based on central sensitization	Pharmacologically based drug therapy	Combination of drug therapy and other therapies based on synaptic plasticity
Other	Advocated the importance of a biopsychosocial understanding in treatment	Emphasized the influence of the financial aspects of drug development on treatment, and mentioned the efficacy of treatment with multiple drugs rather than monotherapy	Advocates a general treatment method for symptoms formerly classified as chronic illness syndrome

Chapter 3

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