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Neurochemistry in the Pathophysiology of Septic Encephalopathy

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1. Introduction

Neurochemical studies clarify scientific mechanisms for neurochemicals in the nervous system. These include identification and characterization of neurotransmitters and neuromodulators supportive for neurotransmission in neuronal and glial cells networks in the brain. Neurochemicals based on neural mechanisms have been explained by the ongoing evolution of scientific techniques. These neurochemical techniques include immunohistochemistry, immunoblotting using species’ specific antibodies or radio-labeled substances, etc. And these techniques with electrophysiological methods will be powerful tools to describe the pathophysiological mechanisms of sepsis-related brain dysfunction.

Neurochemical techniques are useful to examine the physiological mechanism of normal brain function such as synaptic transmission, plasticity and neurogenesis. On the other hand, these techniques are available to find pathogenesis of the brain. In this chapter, we’d like to focus on the brain pathophysiology, which is often confronted in an intensive care unit, ‘septic encephalopathy’.

In normal condition, our brain is protected for its environment such as neurochemical balance by the barrier called ‘blood brain barrier (guardian of the brain)’. However, sepsis leads to the impairment of blood brain barrier function (i.e., enhancement of permeability through blood brain barrier) and imbalance of neurotransmission. In addition, following sepsis, apoptotic signaling pathway is activated (Hotchkiss RS & Nicholson DW, 2006) and/or chemical mediators passing through disrupted blood brain barrier lead to necrotic neuronal cell death accompanying with ischemia (Sharshar T et al, 2004) and edema (Kafa IM et al, 2007). These phenomena finally lead to the imbalance of brain activity after septic encephalopathy.

Next section, we introduce the neurochemical techniques in terms of the contents: 1) what are pathophysiological phenomena in sepsis and its related encephalopathy in combination
of inflammatory response, 2) how to examine the aberrant brain function, 3) what is the future for sepsis research.

2. Sepsis

2.1 Pathogenesis of sepsis

2.1.1 Symptoms

Sepsis is a systemic inflammatory state in the whole body by bacteria infection in the blood stream (i.e., systemic inflammatory response syndrome) (Bone RC et al, 1992). In systemic inflammatory response syndrome, the innate immune systems are overactivated. The systemic inflammatory response syndrome is characterized by the symptoms such as fever and hypotension in patients. In severe sepsis pathology, immunohistochemical studies using both of postmortem human and an animal model of sepsis in rodents reveal the brain ischemia (Sharshar T et al, 2004), edema (Pfister D et al, 2008), hemorrhage (Casanova E et al, 2001) after sepsis. On the other hand, following sepsis, several kinds of symptoms such as polyneuropathy are also observed. These symptoms enhance complexity of the septic pathophysiology (Bolton CF et al, 1993; Nauwynck M & Huyghens L, 1998). Hence, the septic conditions include neurological symptoms.

2.1.2 Molecular mechanisms

Molecular mechanism of immunology for sepsis is investigated. When pathogen (bacteria etc.) is invaded into the blood stream, it is recognized to be pathogen-associated molecular pattern such as lipopolysaccaride, bacterial component in immunological dendritic cells and T cells. When the pathogen-associated molecular pattern binds to toll-like receptor, the toll-like receptor facilitates cytokine release (Kim KD et al, 2007). After the cytokine release, the septic condition triggers downstream signaling pathways. These pathways translocate and activate NF-kappa B in the nucleus through I-kappaB degradation and mitogen-activated protein kinase (MAPK) and JUN kinase activation. Finally, NF-kappaB drives transcription of interleukin family (interleukin -1, 2, 6, 8 and 12) and tumor necrosis factor-α.

2.1.3 Cytokine storm

These activations lead to be cytokine storm (Harrison C, 2010). In fact, 30% of septic patients have serious symptoms without bacteremia in their blood (Sprung CL et al, 1990). The result suggests that after removal of bacteria, cytokine storm is a major factor for the tissue injury after severe sepsis. What is a player for accelerating cytokine storm? Recent finding suggests that small protein ‘complement’ creates cytokine storm (Ward PA, 2010). The complement serves as a supportive factor to enhance the efficacy of antibodies in order to clear pathogen in the blood. The complement C5a has their receptors, C5aR and C5L2, in the pituitary and their receptors are up-regulated after sepsis. C5a is also performed as a central hub to activate various inflammatory responses including disseminated intravascular coagulation, systemic inflammatory response syndrome, lethal bacteremia, immunosuppression, septic shock and heart failure (Rittirsch D et al, 2008). Conversely, when the C5a is neutralized by specific antibody, blood brain barrier disruption and
pituitary dysfunction in severe sepsis is alleviated in the rat (Flierl MA et al, 2009). Hence, C5a will be a hopeful target for cytokine storm regulation after sepsis.

### 2.1.4 Multiple organ dysfunction syndrome

Because of the amplification of systemic inflammatory states after sepsis, without appropriate intensive care including antibiotic therapy, vasopressor medications, mechanical dialysis (Dellinger RP et al, 2008), systemic inflammatory response syndrome and cytokine storm then lead to be multiple organ dysfunction syndrome. Once sepsis is reached to multiple organ dysfunction syndrome, the patients are destined to be coma or delirium. Multiple organ dysfunction syndrome implicates in the pathogenesis of septic encephalopathy.

### 2.2 Septic encephalopathy

Septic encephalopathy is devastating syndrome results from systemic inflammatory response syndrome in sepsis. In patients after multiple organ dysfunction syndrome, septic encephalopathy is appeared. The symptoms of septic encephalopathy patients are characterized as long-term cognitive impairment including deficits in memory, attention, concentration of consciousness (Streck EL et al, 2008). Why do these symptoms occur?

A lot of research groups have performed to tackle and continue the challenging to uncover the mystery of septic encephalopathy. Typical characteristic in septic encephalopathy is that the chemical substances in the whole body can access to the neuronal function in the brain after blood brain barrier (a guardian of brain) disruption. In fact, we find that occludin, the marker for tight junction, is drastically reduced in the mouse brain after septic encephalopathy (Imamura Y et al, 2011). This may cause the edema after septic encephalopathy (Papadopoulos MC et al, 1999). Then, what is the pathophysiology in the neurochemical substances related to septic encephalopathy?

Several decade ago, several lines of research reports have been addressed for the possibility of neurotransmitters imbalance in septic encephalopathy. One of the possible suggestions to septic encephalopathy-induced abnormalities stems from amino acid derangements in septic patients (Freund HR et al, 1978). The altered patterns of plasma amino acids are well correlated between non-septic encephalopathy and severe septic encephalopathy groups (Freund H et al, 1979). For example, several amino acids including glutamate, aspartate and tryptophan are altered in septic encephalopathy patient. These amino acids serve as neurotransmitters or are utilized for synthesis of neurotransmitters. Furthermore, using an animal model of septic encephalopathy, it is also suggested that these amino acid alteration affect the neurotransmitter in the brain. After cecal ligation and puncture, an animal model of septic encephalopathy, in rat, neurotransmitters serotonin and norepinephrine are altered and the altered patterns are correlated with these differences of amino acids (Freund HR et al, 1986). Hence, monoamine neurotransmitters are aberrant in septic encephalopathy. In addition, as shown in the following section, glutamatergic neurotransmission may be also affected and synaptic plasticity is disturbed (Imamura Y et al, 2011). Altogether, a whole body inflammation after sepsis 1) leads to blood brain barrier disruption, 2) affects the neurotransmitter levels and 3) may lead to be the symptoms of septic encephalopathy.
3. Scientific techniques of neurochemistry: How to see synaptic mechanism in septic brain

3.1 General mechanism of synaptic transmission in the brain

Neurochemical studies have been performed to clarify the temporal and spatial distribution of substances (i.e., proteins, enzymes, etc.) in brain. In the brain, neuronal cells which are major components of nervous system including brain, spinal cord constitute synapses. When the neurons are electrically excitable, neurotransmitters are released from the terminal of neuronal synapses (i.e., pre-synaptic terminals). On the other hand, the other neurons which receive the neurotransmitters possess receptors (i.e., post-synaptic terminals). The receptors binding to neurotransmitters activate electrically post-synaptic neurons and thereby the neuronal information is processed in the brain (i.e., synaptic transmission). Furthermore, the synaptic transmission is modulated by various chemical mediators (i.e., carbon monooxide (CO), nitric oxide (NO) etc.). These mediators are also critical to induce synaptic plasticity (i.e., plastic changes of electrical strength or efficacy in synaptic transmission). Hence, the neurotransmitters such as glutamate, acetylcholine and monoamine are major neurochemical substances, furthermore, these chemical mediators are necessary for normal synaptic transmission and synaptic plasticity. Aberrant expressions of these neurochemicals impede on the synaptic functions.

3.2 Sepsis affects synaptic receptor and its modulator

After sepsis, synaptic transmission seems to be affected. Although, to date, no reports are found for the direct evidence for the aberrant synaptic transmission by sepsis, sepsis-induced inflammatory cytokine alters the synaptic function. For example, interleukin-1β, which is up-regulated after sepsis, inhibits the expression of excitatory neurotransmitter receptors such as N-methyl-d-aspartate (NMDA) receptor (Coogan A & O'Connor JJ, 1997) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (Lai AY et al, 2006). Conversely, interleukin -1β enhances the expression level of inhibitory neurotransmitter receptor, gamma-aminobutyric acid (GABA) receptor (Serantes R et al, 2006). In addition, NO synthase (NOS) were up-regulated after endotoxemia (El-Mas MM et al, 2011). These neurochemicals and their receptors are critical for synaptic transmission and plasticity. These findings suggest that the sepsis-induced downstream effects such as interleukin (i.e, cytokine) are possibly associated with imbalance of synaptic transmission and its plasticity.

3.3 Neurochemical methods to uncover the effect of sepsis

Our research group is challenging to tackle this issue (Imamura Y et al, 2011). To examine this, an animal model of sepsis is used. The methods are ‘cecal ligation and puncture’ and ‘intraperitoneal injection of lipopolysaccharide (i.e., cell wall of gram negative bacteria)’. Compared to sham-operated animals (i.e., surgical operation without cecal ligation and puncture or intraperitoneally injected saline’, the difference is determined by biochemical assays.

To visualize the dynamics of neurochemicals between the sham-operated mice and septic mice, our methods are 1) immunohistochemistry, 2) immunoblotting, 3) electrophysiology. These methods are well-established to examine the pathological condition by comparing with normal condition and its effect in animal models. For 1) immunohistochemistry, the
procedure is summarized in Figure 1A. In brief, immunohistochemical staining is usually performed in following steps: 1) septic brain is fixed in 1-4% paraformaldehyde solution in

Fig. 1. Experimental procedure. A, immunohistochemistry. B, immunoblotting
phosphate buffered saline (PBS, pH = 7.2-7.4), 2) the brain is immersed in sucrose suspension for dehydration, embedded in optical cutting temperature compound and frozen in -80°C until use, 3) incubation with bovine serum albumin or serum solution to prevent non-specific binding of antibody which augments the background noise, 4) very thin brain slices (10 µm thick) are incubated with suspension including 1/100 -1/500 concentration (it depends on the specificity of antibody) of primary antibodies, 4) secondary antibodies which illuminate specific wavelength (usually 300-700nm) to visualize the spatial distribution of the proteins. Statistical analyses are performed between sham-operated groups and septic groups under normalization of each signal intensity and area by the number of cells (using nuclei staining).

Difference of amount of specific proteins after sepsis can be determined by immunoblotting (Figure 1B). Following suspension of tissue samples with homogenizer, the amount of total proteins in the brain mixture is measured by bradford protein assay for normalization between sample amounts. Then, the proteins are loaded with polyacrylamide gel electrophoresis. Amount of the subject protein samples transferred to PVDF membrane are determined by the specific primary antibody and the band intensities visualized by the enzyme, horse radish peroxidase, secondary antibody.

Brain function was determined by electrophysiology. Field excitatory post-synaptic potentials (fEPSPs) recordings detect population neuronal activity from recording electrode placed in extracellular neurons. Since, the method is available when neurons are arranged coordinately, it is useful for study of long-potentiation (LTP). For LTP study, our research group uses following methods: 1) making brain slices including hippocampus (300 µm thick) and maintaining them in perfusing solution (2-3 ml/min) of artificial cerebrospinal solution (ACSF) saturated with mixture gas of 95% oxygen and 5% carbon dioxide, 2) the hippocampal slices are transferred to the recording chamber and placed, 3) stimulation electrode is placed on perforant path fiber and recording is performed from neurons in dentate gyrus, 4) LTP is induced by the high frequency stimulation (100 Hz for 1sec x 4times, interval 5min)(Figure 2).

As a result, we find that endotoxemia after cecal ligation and puncture results in occludin (i.e., a marker for blood brain barrier) disruption (Figure 3), increased interleukin-1β on microglial cells in the hippocampus of the brain (Figure 4) and up-regulated interleukin-1β receptor on neurons (Figure 5).

Importantly, LTP is unable to induce in a group of septic mice (Figure 6B). Several lines of studies indicate that interleukin-1β inhibits LTP (Katsuki H et al, 1990; Ross FM et al, 2003). Due to these suggestions, we apply interleukin-1β antagonist before LTP induction. Interleukin-1β antagonist effectively cancels LTP deficiency after cecal ligation and puncture (Figure. 6C). These findings strongly suggest that increased interleukin in the brain after sepsis results in synaptic plasticity deficiency. Our approach successfully demonstrates the synaptic functional deficiency in septic encephalopathy and relevance of interleukin antagonist for the deficiency. However, there are still unclear for the following points: 1) effects of other inflammatory mediators, such as high mobility group box (HMGB)-1 (Zhao X et al, 2011) and tumor necrosis factor (Clark IA et al, 2010) which are expressed abundantly in the brain, to synaptic function, 2) How is the consequence of sepsis on the other brain regions except hippocampus. In following section, relevance of autonomic nervous system and a novel technology for the treatment and prescription of septic encephalopathy in the future are discussed.
Fig. 2. Long-term potentiation (LTP) in the hippocampal slices. A, hippocampal slices from mouse brain. B, LTP is induced by high frequency stimulation (100Hz for 1sec x 4 times, 5 min interval).
4. Cholinergic anti-inflammatory pathway

Sepsis affects autonomic systems (Tracey KJ, 2002). In lipopolysaccharide-injected rat (i.e., an animal model of sepsis), electrical threshold to induce action potentials are increased (i.e., hard neuronal firing) in vagus nerve (Huang J et al, 2010). This finding suggests that the vagus nerve activity is reduced after sepsis. Conversely, when the vagus nerve is electrically charged by external stimulation electrode, sepsis is alleviated (Huston JM et al, 2006; Rosas-Ballina M et al, 2008; Vida G et al, 2011). The vagus nerve projects parasympathetic neurons to all organs except adrenal gland and controls acetylcholinergic synaptic transmission. Wang and colleagues, using α7-subunit of acetylcholine receptor knockout mice, demonstrate that vagus nerve stimulation inhibits excess release of tumor necrosis factor (i.e., activator of inflammatory mediator) in wild-type mice but not in acetylcholine knockout mice (Wang H et al, 2003). In addition, vagus nerve stimulation inhibits organ injury in the lung (Boland C et al, 2011), gut (Eisner F et al, 2011), spleen (Vida G et al, 2011) after sepsis. Furthermore, excess release of high mobility group box (HMGB)-1...
Fig. 4. Up-regulation of interleukin (IL)-1 on Iba1-positive cells after cecal ligation and puncture (CLP). (A) Staining of IL-1β immunoreactivity (green), Iba1 (marker for microglial and/or macrophage phagocytosis) immunoreactivity (red), and DAPI (nuclei, blue) in hippocampus from sham-operated mice (left panels) and CLP-treated mice (right panels). Magnified view shown in the lower right-hand corner. Merge: white arrow heads in higher magnification indicate Iba1 positive cells in the IL-1β positive cells. Scale bar: 200 μm (lower magnification), 50 μm (higher magnification). Higher intensity of IL-1β (B) and Iba1 (C) is seen in CLP mice. (D) The ordinate shows the percentage of Iba1-positive cells in the IL-1-positive cells. The numbers of immunopositive cells were counted between slices, respectively. Almost all (>80%) IL-1-positive cells are Iba1-positive after CLP. Bar represents mean±SEM; (n=7: sham, n=6: CLP-treated). * P<0.01 (Student t-test). (from Imamura et. al, (2011))
Fig. 5. Increased interleukin (IL)-1 receptor on hippocampal neurons after cecal ligation and puncture (CLP). (A) Triple staining of DAPI, type 1 IL-1 receptor (IL-1R1) and NF200. Blue: DAPI, green: IL-1R1, red: NF200. Magnified view shown in the lower right-hand corner. Merge: white arrow heads in higher magnification indicate NF200 positive cells in the IL-1R1 positive cells. Scale bar: 200 µm (lower magnification), 50 µm (higher magnification). (B) Slight decrease in neuronal fibers after CLP. (C) Increased IL-1R1 intensity after CLP. (D) Almost all (>90%) IL-1R1s are distributed on neurons. Bar represents mean±SEM; (n=7: sham, n=6: CLP-treated). * P<0.01 (Student t-test). (from Imamura Y et. al, (2011))
Fig. 6. Septic encephalopathy (SE) results in long-term potentiation (LTP) deficiency by interleukin (IL)-1β. (A) Successful rates of recording of field excitatory post-synaptic potentials (fEPSP) from sham-operated mice and cecal ligation and puncture (CLP)-treated mice. Hippocampal perforant-path fibers were stimulated with test pulse stimulation (30-s intervals, 200-μs duration, half-maximum intensity). fEPSP was recorded at the dentate gyrus at a distance of 300 μm from the stimulation electrode (P<0.002, Student t-test). (B) Schematic showing LTP deficiency after CLP. LTP experiments after CLP were performed according to the schematic, which shows the time course of the experimental procedure. LTP was induced by high-frequency stimulation (100 Hz x 1 s, four times, at 5-min intervals indicated by the arrows). Representative traces of baseline at t = 0 min and LTP at t = 80 min are shown. Black trace: baseline fEPSP, red trace: fEPSP after LTP. (C) Schematic showing cancelation of LTP deficiency in CLP-treated mice by IL-1R antagonist (IL-1ra). Brain slices were incubated in the presence of IL-1ra for 30 min before LTP recording. Note that IL-1ra is effective for LTP recovery after CLP, and IL-1ra reagent has no effect on fEPSP amplitudes. Bar represents mean±SEM; (n = 7: sham, n = 7: CLP-treated). * p < 0.01 (Student t-test). (from Imamura et. al, (2011))
(i.e., inflammatory mediator) from macrophage is also inhibited by vagus nerve stimulation (Wang H et al, 2004). The neural mechanism of vagus nerve stimulation is summarized in review (Tracey KJ, 2009). The review describes the mechanisms as follows: when sepsis is induced by endotoxemia, a site of infection imposes cytokine release through NF-kappaB (nuclear factor kappa-light-chain enhancer of activated B cells) activation. This signaling pathway accelerates cytokine production and thereby cell death via cytokine storm. When the vagus nerve from the brain stem is stimulated, it activates cholinergic anti-inflammatory pathway (efferent arc) and inhibits innate immune response in the spleen via activation of nicotinic acetylcholine receptor. The nicotinic acetylcholine receptor activation suppresses NF-kappaB activation via JAK2 (Janus kinase 2, cytokine receptor) - STAT3 (signal transducer and activator of transcription 3, transcription activator) pathway and the cytokine release.

Hence, vagus nerve stimulation may employ a high potential for the therapeutics of the clinical treatment of sepsis-related systemic inflammatory symptoms of septic encephalopathy.

5. Future prospect: A novel technology for tracking one molecule imaging in living organism

The findings we introduce are mainly resulted from neurochemical research assays using dissected tissues and cells. Recently, non-invasive methods such as functional magnetic resonance imaging (fMRI) are utilized to examine the brain dysfunction in living organism (rodents and human, etc). For example, in a mouse model of sepsis, accumulation of effusion by vasogenic edema is observed using fMRI in hippocampus and cortex (Bozza FA et al, 2010). Thus, fMRI is a powerful tool to find the damaged region in the brain because of the high spatial resolution. However, since fMRI detects the alteration of blood stream and estimates this as brain functional alteration, there is a limitation of the fMRI study. For example, it is hard to distinguish excitatory or inhibitory neurotransmission without a tag of each. In addition, because action potentials propagation between synapses in the brain is conducted within 100 msec (Wu JY et al, 2008), it is hard to track the temporal alteration of fast synaptic transmission with the time resolution (later than 1s) of fMRI (Tsao J, 2010). To reinforce these weak points, we address a novel nano-technology, ‘one molecule imaging with quantum dot’ for the future research of septic encephalopathy.

A quantum dot (q-dot) is a nanometer-sized semiconductor particle (2-10 nm diameter). Cadmium selenide (CdSe) and cadmium telluride (CdTe) are well-utilized for the nano-materials of q-dot. When q-dot is placed in the crystallized structure, its electrical state for the fluorescence emission is discretized (Reed MA et al, 1988). As a result, only the fluorescence with a specific wavelength is amplified. Immunohistochemical studies using q-dot have a high signal to noise ratio and few photobleaching(Chan WC, Nie S, 1998). Although normal q-dots are hydrophobic, it can be changed their property to hydrophilic in order to apply to living organism. Jin T et. al (2008) develop a water-soluble glutathione-coated Q-dots. They successfully detect q-dot signals in the lymph node in the mouse (Fig. 7). In addition, q-dot is available to track the molecules expressed in the brain. Intraperitoneally-injected q-dots can be found in the brain (Kato S et al, 2010; Yeh TK et al, 2011). Hence, q-dot is a hopeful nano-material to track a molecule associated with sepsis.

Then, how do we track the molecules associated with septic encephalopathy with q-dots?
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Near infrared spectroscopy (NIRS) uses near infra-red region (800-2500nm) of light. Since the light in near infra-red range can pass through the skull, reach to the surface of the brain and coincide with the fast event-related responses in human recorded by electroencephalograms (Medvedev AV et al, 2010), it has been used to track cerebral hemodynamics (Gratton E et al, 2005) and human brain activity (Perrey S, 2008). On the other hand, trials to apply q-dots to the molecules associated with pathological states are performed in neurosurgery (Taghva A et al, 2010) and brain tumor (Popescu MA & Toms SA, 2006). Therefore, if labeling of brain with q-dot which emits the fluorescence light in the near infra-red region becomes successful, we can track the molecules associated with septic encephalopathy in higher temporal resolution in the future studies.

6. Conclusion

Septic encephalopathy is associated with many kinds of inflammatory cytokines, receptors, chemicals such as interleukin family, toll-like receptor, tumor necrosis factor, high mobility group box. Since these inflammatory molecules induce systemic inflammatory response in the whole body and affect the brain function after blood brain barrier disruption, they occurs neurological symptoms such as vasogenic edema, aberrant synaptic transmission and plasticity. In addition, the weakness of vagus nerve after septic encephalopathy is related to the pathophysiology. Although the molecular mechanisms for sepsis are explained, medical

Fig. 7. Lymph node imaging by near infra-red q-dot (from Jin T. (2008))
intervention for patients of septic encephalopathy in intensive care unit is largely limited to symptomatic treatment. The reason is that spatial and temporal dynamics of the functional molecular patterns in various organs for the cause of septic symptoms are still not fully described. For the future medical treatment of septic encephalopathy, we address the two possibilities. First, to find the spatial and temporal dynamics of molecules, q-dots labeled with molecules for septic encephalopathy are recorded with both of near infra-red spectroscopy and functional magnetic resonance imaging. Second, to alleviate the symptoms, it may be effective to stimulate the vagus nerve with non-invasive method, since vagus nerve stimulation can reduce the excess inflammatory cytokine release by mechanisms of nicotinic acetylcholine receptor activation, which inhibits apoptotic and necrotic pathway of cells and tissues after sepsis. These novel approaches will progress the intervention for the sepsis and its encephalopathy in the future studies.

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8. References


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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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