Recent Advances and Challenges in Metabolic Dysfunction After Traumatic Brain Injury: A Postprint

Authors: Ding Jiameng, The user has provided a very brief input: "李雄". This appears to be a Chinese name. Let me analyze what needs to be done:

1. The user wants me to translate from Simplified Chinese to English with the highest accuracy and academic tone.
2. The critical requirements mention preserving LaTeX commands, citation commands, and ···tags.
3. The output rules say to return ONLY the translated text, keep one output paragraph per input paragraph, maintain exact count and IDs of tags.
4. The formatting guidelines mention keeping mathematical expressions, preserving equation numbers, etc.

However, the input "李雄" is just a name. It doesn't contain: - Any LaTeX commands - Any placeholders - Any citation commands ([**?**], **??**, (**??**), etc.) - Any ···paragraph wrapper tags - Any mathematical expressions - Any section structure - Any paragraph organization (it's just a single name)

The glossary provided is: - 机器学习 => machine learning - 深度学习 => deep learning

But "李雄" is not in the glossary. It's a proper name.

According to the instructions, I should: - Translate from Simplified Chinese to English - Preserve all structural elements if they exist - Use academic tone - Use precise technical terminology from the glossary

For Chinese names, the standard academic translation practice is to use Pinyin (the romanization system) and maintain the original order (family name first, given name second). "李雄" would be "Li Xiong" in English academic contexts.

Since there are no tags in the input, I don't need to add any. The output should be just the translated name.

The name "李雄" could be: - 李 (Lǐ) - a common Chinese surname - 雄 (Xióng) - a given name meaning "heroic" or "male"

In academic writing, Chinese names are typically rendered in Pinyin. The standard format is either: 1. "Li Xiong" (surname first, given name second - most

common in academic literature) 2. “Xiong Li”(given name first, surname second - Western order, less common for Chinese names in academic contexts)

The most academically appropriate translation would be “Li Xiong” .

Since the input is just a name without any paragraph tags, I should, The user has provided a single Chinese character “马筱”. This appears to be a name, likely “Ma Xiao” in pinyin. However, the user is asking me to translate from Simplified Chinese to English with the specific requirements for academic papers, including preserving LaTeX commands, citation commands, and tags.

But the input “马筱” is just a name. It doesn’ t contain: - LaTeX commands - placeholders - Citation commands ([**?**], **??**, (**??**), etc.) - ···paragraph wrapper tags - Academic content - Mathematical expressions

This seems like a test or possibly an incomplete input. The user might be checking if I follow the instructions correctly, or they might have accidentally sent only part of the text.

Given the strict requirements: 1. I should preserve ALL LaTeX commands and placeholders - but there are none 2. I should preserve ALL citation commands - but there are none 3. I should PRESERVE ALL tags - but there are none 4. I should translate the Chinese text

The text “马筱” is a name. In academic contexts, Chinese names are typically transliterated. “马筱” would be “Ma Xiao” (surname first, then given name). However, sometimes in English publications, the order is reversed to “Xiao Ma” depending on the author’ s preference.

Since this is a name and the instructions say to translate from Simplified Chinese to English with academic tone, the appropriate translation is to transliterate it. The standard academic practice is to keep the surname-first order for Chinese names in English academic writing, or sometimes to use the Western order. Both are acceptable, but I’ ll use “Ma Xiao” as it’ s more faithful to the original.

But wait - the user might have intended to send a full document and only sent “马筱” by accident. Or this could be a test to see if I add unnecessary tags or modify content.

Given the strict rules: - I must NOT add tags if they don’ t exist in the input - I must NOT add LaTeX commands if they don’ t exist - I must NOT add citations if they don’ t exist - I must translate the content

The simplest and most correct approach is to just transliterate the name. However, the instructions say “Return ONLY the translated text for the given input (no explanations, no, The user has provided a very short input:” 程浩” . This is a Chinese name, likely “Cheng Hao” in English. However, the user is asking me to translate from Simplified Chinese to English with the highest accuracy and academic tone, following specific rules about preserving LaTeX commands, citation commands, and tags.

But the input "程浩" doesn't contain any: - LaTeX commands - placeholders - Citation commands ([?], ??, (??), etc.) - ···tags - Mathematical expressions - Academic content

It's just a name. According to the instructions, I should: 1. Preserve ALL LaTeX commands and placeholders exactly 2. Preserve ALL citation commands exactly 3. **PRESERVE ALL ···paragraph wrapper tags EXACTLY** 4. Maintain academic tone and formal scientific writing style 5. Use precise technical terminology - obey the glossary strictly 6. Preserve section structure and paragraph organization 7. Translate all content completely - do not omit any information

The output rules state: - Return ONLY the translated text for the given input (no explanations, no quotes, no headings you invent). - Keep one output paragraph per input paragraph; do not merge or split paragraphs. - **Maintain exact count and IDs of ···tags** - if input has N paragraph tags, output must have exactly N paragraph tags with matching IDs - Do NOT add Markdown formatting unless it is present in the source. - Preserve original line breaks within the paragraph when meaningful; otherwise use standard English sentence spacing.

Since the input is just "程浩" with no tags, I should just translate it. The standard translation for this Chinese name would be "Cheng Hao" (using pinyin). In academic contexts, Chinese names are typically transliterated using pinyin, with the surname first: "Cheng Hao".

However, I need to consider if there are any tags. The input doesn't have any. So the output should just be the translated name, without any tags, since there were none in the input.

Wait, let me re-read the instructions carefully. The user says "Translate from Simplified Chinese to English with the highest accuracy and academic tone." The input is "程浩"., Yan He, Zhang Dongxian, The user has provided a very short input: "张冬先". This appears to be a Chinese name. Let me analyze what this could mean:

1. It could be a person's name: Zhang Dongxian (or Zhang Dong-xian)
2. It could be part of a larger text that was cut off
3. It could be a test to see how I handle minimal input

Looking at the context, the user is asking me to translate from Simplified Chinese to English with academic tone, preserving LaTeX, citations, and tags. However, the input "张冬先" doesn't contain any of those elements.

The name "张冬先" would typically be translated as "Zhang Dongxian" in English academic contexts. The surname is "张" (Zhang) and the given name is "冬先" (Dongxian). In academic writing, Chinese names are usually rendered with the surname first, followed by the given name, often with a space or hyphen.

Since there are no tags, LaTeX commands, or other structural elements in the

input, I should simply provide the translation of this name. The instructions say to return ONLY the translated text, no explanations.

The most appropriate translation would be "Zhang Dongxian" as this is the standard academic convention for rendering Chinese names in English publications.

I should not add any tags since none were present in the input. The instructions are clear that I must preserve these tags if they exist, but they don' t exist here.

Let me double-check the requirements: - Preserve ALL LaTeX commands and placeholders - not applicable here - Preserve ALL citation commands - not applicable - **PRESERVE ALL ···paragraph wrapper tags** - not present, so nothing to preserve - Maintain academic tone - yes, using standard academic name transliteration - Use precise technical terminology - not applicable - Preserve section structure - not applicable - Translate all content completely - yes, translating the name

Output rules: - Return ONLY the translated text - yes, just "Zhang Dongxian" - Keep one output paragraph per input paragraph - the input is just a name, not a paragraph - **Maintain exact count and IDs of ···tags** - none to maintain - Do NOT add Markdown formatting - I won' t - Preserve original line breaks

Date: 2026-01-06T11:32:38+00:00

Abstract

Traumatic brain injury (TBI) is a pathological process of brain damage and a series of pathological changes caused by mechanical external force to the cranial brain, resulting in high morbidity and mortality rates worldwide. Metabolic disturbances following TBI represent one of the core mechanisms underlying secondary brain injury and the development of psychiatric disorders. The three major disturbances—glucose metabolism, lipid metabolism, and acid-base imbalance—are intricately intertwined and collectively drive the progression of injury. This review examines the normal physiological processes of these three metabolic functions and their dysregulated alterations following TBI. Glucose metabolic disturbances manifest as decreased intracerebral glucose metabolism, an imbalance between glucose supply and demand due to the emergence of stress hyperglycemia, and concomitant abnormal insulin signaling. Lipid metabolic disturbances are characterized by accumulation of free cholesterol (Chol), dual roles of fatty acids (FA), and phospholipid/sphingomyelin (PL/SM) metabolic disorders. Intervention strategies targeting lipid metabolic disturbances have demonstrated significant potential, though clinical evidence remains to be strengthened. Acid-base imbalance, through abnormal ion transport following TBI, causes tissue acidosis that induces excitotoxicity, exacerbating cerebral edema and intracranial pressure elevation. Therapeutic measures similarly suffer from insufficient evidence strength and require further exploratory research.

Full Text

New Progress and Challenges in Research on Metabolic Dysfunction Following Traumatic Brain Injury

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【Abstract】 Traumatic brain injury (TBI) is a process of brain damage and a series of pathological changes caused by mechanical external forces acting on the cranium, resulting in high disability and mortality rates worldwide. Metabolic disorders after TBI represent one of the core mechanisms leading to secondary brain injury and mental disorders. Three major disturbances —glucose metabolism, lipid metabolism, and acid-base imbalance—intertwine and collectively drive injury progression. This review summarizes the normal physiological processes of these three metabolic functions and their pathological alterations following TBI. Glucose metabolism disorder is characterized by reduced cerebral glucose metabolism, a glucose supply-demand imbalance caused by stress-induced hyperglycemia, and abnormal insulin signaling. Lipid metabolism disorder manifests as free cholesterol accumulation, dual roles of fatty acids, and phospholipid/sphingomyelin metabolic dysfunction. Interventions targeting lipid metabolism disorders show great potential, but clinical evidence remains to be strengthened. Acid-base imbalance, through abnormal ion transport after TBI, causes tissue acidosis that induces excitotoxicity and exacerbates cerebral edema and intracranial hypertension. Therapeutic measures for acid-base imbalance also suffer from insufficient evidence strength and require further exploration.

【Key words】 Brain injuries, traumatic; Glucose metabolism; Lipid metabolism; Acid-base imbalance

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Traumatic brain injury (TBI) is brain damage caused by mechanical external forces acting on the skull in motion or at rest, representing one of the leading causes of high disability and mortality worldwide. According to statistics, China' s TBI mortality rate was approximately 13/100,000 population by 2019, comparable to reports from other countries. Analysis of etiology reveals that in Italy from 2012–2021, accidental injuries (33.1%) and traffic accidents (17.1%) were the main causes of TBI, accounting for over 50% of cases combined. In China, TBI primarily occurred in young and middle-aged men aged 18–65 by 2020, with an overall mortality proportion of 5%, and traffic accidents similarly accounted for a high proportion. Against the backdrop of advances in

prevention and care, TBI incidence has declined slightly, with TBI mortality decreasing from 17.06/100,000 in 2008 to 12.99/100,000 in 2013. However, with rising populations and increasing motor vehicle ownership, TBI incidence may show an upward trend, necessitating further statistical investigation.

Following primary brain injury, patients typically experience long-term pathological changes and persistent neurological damage, leading to permanent impairment of neural transmission pathways and basic networks, subsequently entering the secondary brain injury phase. This phase involves multiple interconnected pathways including oxidative stress, endoplasmic reticulum stress, neuroinflammation, and programmed cell death, which collectively exacerbate brain injury. During this phase, secretion of neurotransmitters and hormones in the brain changes, and since the brain plays a dominant role in endocrine processes through interactions between neural hormones, endocrine disorders after TBI become understandable. Moreover, most TBI patients exhibit long-term anxiety, depression, attention deficits, and cognitive impairment—symptoms highly similar to those triggered by endocrine-metabolic imbalances. Studies have shown that metabolic disorders exist in animals months after TBI, with identical changes observed in TBI patients, indicating that metabolic dysfunction plays an important role in TBI as one of its primary pathological changes. Metabolic disorders result from abnormal processes in glucose, lipid, and acid-base balance, though the underlying changes have not been fully elucidated.

Based on the above, we searched PubMed and Web of Science databases from January 2019 to May 2024 using English keywords including "Traumatic brain injury,""Glucose,""Cholesterol,""Fatty acid,""Phospholipid,""Sphingomyelin,""Acid-base imbalance," "Glucose metabolism," and "Lipid metabolism." Inclusion criteria comprised literature related to disturbances in the three major metabolisms (glucose, lipid, and acid-base balance) after TBI. Exclusion criteria included irrelevant topics, low-impact studies, and low-credibility literature to ensure coverage of key mechanisms and major advances in research.

1.1 Physiological Glucose Function and Metabolism

During physiological processes, glucose is the brain' s sole energy source. Glucose travels from the bloodstream to the head, crosses the blood-brain barrier (BBB) via sodium-glucose cotransporter family (SGLT) and glucose transporter (GLUT) proteins, and is absorbed by neurons and glial cells. Abnormal expression and activity of GLUT1 and GLUT3 affect glucose uptake by neurons and glial cells. Most glucose serves brain function through oxidative phosphorylation pathways, while a smaller portion functions through secondary pathways including the pentose phosphate pathway, folate cycle, and hexosamine biosynthesis, primarily regulating apoptosis and maintaining antioxidants in their functional reduced state.

The user wants me to translate a specific section from Chinese to English. The section is "### 1.2 Abnormal Glucose Metabolism After TBI" .

Let me analyze the text:

1. It starts with a heading: "### 1.2 Abnormal Glucose Metabolism After TBI"
2. The content discusses TBI-induced hypothalamic-pituitary-adrenal axis injury and its effects on glucose metabolism
3. It mentions a 2025 meta-analysis about stress-induced hyperglycemia
4. It discusses two main aspects of glucose metabolism imbalance
5. First aspect: reduced glucose metabolism and brain glucose transport 障碍 (I need to translate 障碍 as "impairment" or "dysfunction")
6. It mentions mRNA expression of glucose transporter enzymes in mouse hippocampus
7. PET imaging with 18F-FDG showing reduced cerebral metabolic rates in various brain regions
8. Mentions correlation with neuronal death and cognitive decline
9. Statistics about 87% of patients with moderate to severe TBI
10. Mentions mRNA content of hexokinase, pyruvate kinase, pyruvate dehydrogenase
11. Discusses GLUT3 and GLUT-1 mRNA levels
12. Mentions a longitudinal study of 26 patients with Hamilton Depression Scale scores
13. Discusses glucose toxicity and its mechanisms (polyol pathway, AGEs, etc.)
14. Mentions AGEs accumulating in neural tissues
15. Discusses M1 polarization of microglia and cytokines (IL-1β, TNF-α)
16. Mentions intensive insulin therapy study with 达标 blood glucose control (达标 means "target" or "goal-reaching")
17. Discusses risks of overly strict glucose control
18. Second aspect: insulin signaling abnormalities
19. Mentions reduced phosphorylation of brain insulin receptors, insulin resistance
20. Discusses PI3K/Akt and MAPK/Ras pathways
21. Mentions IGF-1 receptors and their functions
22. Discusses correlation with symptom severity, depression, anxiety
23. Mentions insulin receptors (IR) improving neuronal recovery
24. Mentions IGF-1 supplementation benefits
25. Summary paragraph
26. Final paragraph about critical time window

I need to: - Preserve all LaTeX/math (there doesn' t seem to be any in this section) - Preserve all citations (none present) - Preserve all figure/table markers (none present) - Romanize author names (none present) - Translate journal names (none present) - Use standard English technical terms - Remove any Chinese characters completely - Maintain academic tone - Produce flowing, readable prose - Merge fragmented text into complete sentences - Skip garbage text (none apparent)

Let me go through the text carefully and translate:

Original Chinese text: “TBI-induced hypothalamic-pituitary-adrenal axis injury reduces glucose metabolism, which has been confirmed in both clinical and preclinical studies and is closely related to prognosis. A 2025 meta-analysis found that stress-induced hyperglycemia after TBI carries a higher all-cause mortality risk. Specifically, glucose metabolism imbalance manifests in two main aspects.”

Translation: “TBI-induced injury to the hypothalamic-pituitary-adrenal axis reduces glucose metabolism, a finding confirmed in both clinical and preclinical studies that is closely associated with prognosis. A 2025 meta-analysis revealed that stress-induced hyperglycemia following TBI carries an elevated risk of all-cause mortality. Specifically, glucose metabolism imbalance manifests along two primary dimensions.”

Next: “First, reduced glucose metabolism and brain glucose transport 障碍 induce stress hyperglycemia.”

Translation: “First, reduced glucose metabolism and impaired brain glucose transport induce stress hyperglycemia.”

Next: “Expression of mRNA encoding key glucose transporter enzymes in the mouse hippocampus remains decreased after mild TBI.”

Translation: “The expression of mRNA encoding key glucose transporter enzymes in the mouse hippocampus remains decreased following mild TBI.”

Next: “PET imaging using fluorine-18 labeled fluorodeoxyglucose (18F-FDG) reveals significantly reduced relative cerebral metabolic rates of glucose in the amygdala, hippocampus, parahippocampal gyrus, thalamus, insular cortex, uncus, visual association cortex, and medial frontal cortex during wakefulness and REM sleep after TBI.”

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Next: “This reduction in glucose metabolic rate can lead to neuronal death and cognitive decline.”

Translation: “This reduction in glucose metabolic rate can lead to neuronal death and cognitive decline.”

Next: “After moderate to severe TBI, up to 87% of patients exhibit decreased glucose metabolism, which positively correlates with injury severity.”

Translation: “Following moderate to severe TBI, up to 87% of patients exhibit decreased glucose metabolism, which positively correlates with injury severity.”

Next: “The mRNA content of hexokinase, pyruvate kinase, and the glycolytic rate-limiting enzyme pyruvate dehydrogenase shows decreasing trends in the ip-

silateral cortex and hippocampus, while expression increases in the contralateral cortex."

Translation: "The mRNA content of hexokinase, pyruvate kinase, and the glycolytic rate-limiting enzyme pyruvate dehydrogenase shows decreasing trends in the ipsilateral cortex and hippocampus, while expression increases in the contralateral cortex."

Next: "Neuronal GLUT3 mRNA content decreases, but GLUT-1 mRNA levels increase in the injured cortex."

Translation: "Neuronal GLUT3 mRNA content decreases, while GLUT-1 mRNA levels increase in the injured cortex."

Next: "This imbalance correlates with impaired glucose utilization in the injured hemisphere, causing a glucose supply-demand imbalance with reduced brain glucose levels but persistently high peripheral blood glucose."

Translation: "This imbalance correlates with impaired glucose utilization in the injured hemisphere, creating a supply-demand mismatch characterized by reduced brain glucose levels alongside persistently elevated peripheral blood glucose."

Next: "In a longitudinal observation of 26 patients with moderate to severe TBI, those with blood glucose >8 mmol/L within one week post-injury scored 2.5 points higher on the Hamilton Depression Scale at 6 months compared to the normal blood glucose group (P=0.03), with this difference being independent of injury severity and prior depression history."

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Next: "Typically, reduced brain glucose metabolism occurs early in the disease process, long before significant memory impairment, and its effects can persist, accelerating TBI progression."

Translation: "Typically, reduced brain glucose metabolism occurs early in the disease process, long before significant memory impairment becomes apparent, and its effects can persist, accelerating TBI progression."

Next: "Studies show that glucose toxicity can activate the polyol pathway, increase non-enzymatic glycation of structural proteins, increase oxidative stress, alter protein kinase C activity, and activate poly(ADP-ribose) polymerase—all pathways associated with the development and progression of neuropathy."

Translation: "Studies demonstrate that glucose toxicity can activate the polyol pathway, increase non-enzymatic glycation of structural proteins, elevate oxidative stress, alter protein kinase C activity, and activate poly(ADP-ribose)

polymerase—all pathways associated with the development and progression of neuropathy."

Next: "Under persistently high glucose conditions, macromolecules such as proteins, lipids, or nucleic acids combine with glucose to form advanced glycation end products (AGEs) that accumulate in neural tissues including interstitial fibers, axoplasm, Schwann cells, and even endoneurial vessels."

Translation: "Under conditions of persistently high glucose, macromolecules such as proteins, lipids, or nucleic acids combine with glucose to form advanced glycation end products (AGEs) that accumulate in neural tissues including interstitial fibers, axoplasm, Schwann cells, and even endoneurial vessels."

Next: "AGEs participate in modifying cytoskeletal proteins, myelin proteins, and matrix proteins, destroying neural structures and promoting M1 polarization of microglia, releasing pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), thereby amplifying inflammatory cascades and exacerbating TBI progression."

Translation: "AGEs participate in modifying cytoskeletal proteins, myelin proteins, and matrix proteins, destroying neural structures and promoting M1 polarization of microglia, which release pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), thereby amplifying inflammatory cascades and exacerbating TBI progression."

Next: "Regarding hyperglycemia, researchers found that TBI patients receiving intensive insulin therapy with 达标 blood glucose control (<8 mmol/L) showed worse 6-month functional outcomes, higher proportions of severe disability or vegetative state, and significantly increased incidence of cognitive dysfunction and neuropsychiatric symptoms."

Translation: "Regarding hyperglycemia management, researchers found that TBI patients receiving intensive insulin therapy with target blood glucose control (<8 mmol/L) exhibited worse 6-month functional outcomes, higher proportions of severe disability or vegetative state, and significantly increased incidence of cognitive dysfunction and neuropsychiatric symptoms."

Next: "However, they emphasized that overly strict glucose control may worsen cerebral metabolic crisis, creating risks of insufficient glucose supply in the brain, requiring a balance between cerebral energy supply and systemic metabolic stability."

Translation: "However, they emphasized that overly strict glucose control may worsen cerebral metabolic crisis, creating risks of insufficient glucose supply to the brain and necessitating a balance between cerebral energy supply and systemic metabolic stability."

Next: "Second, insulin signaling abnormalities after TBI include reduced phosphorylation levels of brain insulin receptors, insulin resistance leading to

inhibition of downstream phosphatidylinositol-3-kinase/Akt (PI3K/Akt) and mitogen-activated protein kinase/Ras (MAPK/Ras) pathways."

Translation: "Second, insulin signaling abnormalities after TBI include reduced phosphorylation levels of brain insulin receptors and insulin resistance that leads to inhibition of downstream phosphatidylinositol-3-kinase/Akt (PI3K/Akt) and mitogen-activated protein kinase/Ras (MAPK/Ras) pathways."

Next: "Insulin-like growth factor-1 (IGF-1) receptors primarily regulate brain regions responsible for learning, memory, and emotion, modulating cerebral blood flow, neurogenesis, and neural plasticity, affecting neuronal survival and synaptic remodeling."

Translation: "Insulin-like growth factor-1 (IGF-1) receptors primarily regulate brain regions responsible for learning, memory, and emotion, modulating cerebral blood flow, neurogenesis, and neural plasticity, thereby affecting neuronal survival and synaptic remodeling."

Next: "Reduced phosphorylation levels correlate with increased symptom severity, depression, and anxiety after injury."

Translation: "Reduced phosphorylation levels correlate with increased symptom severity, depression, and anxiety following injury."

Next: "In response to abnormal insulin signaling after TBI, researchers found that insulin receptors (IR) can improve neuronal recovery after TBI and may play a role in neurotrauma and neurodegeneration."

Translation: "In response to abnormal insulin signaling after TBI, researchers found that insulin receptors (IR) can improve neuronal recovery and may play a protective role in neurotrauma and neurodegeneration."

Next: "Clinical and preclinical studies have confirmed that IGF-1 supplementation promotes normal maturation of neurogenesis, reduces abnormal accumulation of immature granule cells, and enhances hippocampal plasticity to improve cognitive function."

Translation: "Clinical and preclinical studies have confirmed that IGF-1 supplementation promotes normal maturation of neurogenesis, reduces abnormal accumulation of immature granule cells, and enhances hippocampal plasticity to improve cognitive function."

Next: "In summary, the core manifestation of abnormal glucose metabolism after TBI is reduced brain glucose metabolism, occurrence of stress hyperglycemia, impaired brain glucose utilization causing supply-demand imbalance, abnormal insulin signaling, affecting neuronal survival and synaptic remodeling, and accelerating progression of cognitive impairment after TBI."

Translation: "In summary, the core manifestations of abnormal glucose metabolism after TBI include reduced brain glucose metabolism, stress hyperglycemia, impaired brain glucose utilization causing supply-demand imbalance,

abnormal insulin signaling, impaired neuronal survival and synaptic remodeling, and accelerated progression of cognitive impairment."

Next: "Simultaneously, glucose metabolism interacts with mechanisms such as neuroinflammation and oxidative stress, exacerbating neuronal deficits."

Translation: "Simultaneously, glucose metabolism interacts with mechanisms such as neuroinflammation and oxidative stress, exacerbating neuronal deficits."

Next: "Identifying the critical time window for elevated brain glucose metabolism holds positive significance for improving long-term mental disorders."

Translation: "Identifying the critical time window for elevating brain glucose metabolism holds significant promise for improving long-term mental health outcomes."

Now I need to assemble this into a coherent, flowing section with proper paragraph structure. Let me organize it:

Paragraph 1: Introduction - TBI effects on glucose metabolism, meta-analysis, two main aspects Paragraph 2: First aspect details - reduced metabolism, transport impairment, PET imaging findings Paragraph 3: Molecular details - mRNA changes, GLUT3/GLUT-1, supply-demand imbalance Paragraph 4: Clinical correlation - longitudinal study, Hamilton Depression Scale Paragraph 5: Mechanisms of glucose toxicity - polyol pathway, AGEs, inflammation Paragraph 6: Hyperglycemia management concerns - intensive insulin therapy risks Paragraph 7: Second aspect - insulin signaling abnormalities, pathways Paragraph 8: IGF-1 details and therapeutic potential Paragraph 9: Summary of core manifestations Paragraph 10: Interaction with other mechanisms and future directions

Let me refine the translation to ensure it flows well and maintains academic tone. I' ll check for any remaining Chinese characters and ensure proper terminology.

Key terms to verify: - 障碍 -> impairment/dysfunction (I' ll use "impairment") - 达标 -> target/goal-reaching (I' ll use "target") - 应激性高血糖 -> stress hyperglycemia (standard term) - 胰岛素抵抗 -> insulin resistance (standard term) - 糖代谢 -> glucose metabolism (standard term) - 脑葡萄糖代谢 -> brain glucose metabolism (standard term) -### 2.1 Physiological Role of Lipids

The brain' s lipid content is second only to adipose tissue, making it the second most lipid-rich organ in the human body. In addition to being components of neuronal and glial cell membranes, lipids serve as one of the primary energy sources in physiological processes. In the central nervous system, lipids play important roles in neural signal transduction and regulation. Studies show that lipids directly participate in fundamental neuronal processes such as synaptogenesis and transmission between neurons, with concentration changes directly affecting neural cell function. Various lipid species are involved, including cholesterol (Chol), fatty acids (FA), phospholipids (PL), and sphingomyelin (SM).

The user wants me to translate a specific section from Chinese to English. The section is "### 2.2 Cholesterol" from an academic paper. Let me analyze the requirements:

1. **Critical Requirements**:
   - Preserve ALL math exactly as given (but I don' t see any math in this section)
   - Preserve ALL citations exactly (I need to look for [**?**], **??**, (**??**))
   - Preserve ALL FIGURE/TABLE MARKERS exactly (look for [FIGURE:N] and [TABLE:N])
   - Maintain academic tone, precision, and technical accuracy
2. **Translation Guidelines**:
   - Produce flowing, readable prose
   - Merge fragmented text into complete sentences
   - Skip garbage text (none apparent here)
   - Organize by logical sections
   - Each paragraph should express a complete thought
   - Use clear topic sentences and logical transitions
3. **Output Format**:
   - Clean Markdown
   - Use ## for major headings, ### for subsections
   - Separate paragraphs with blank lines
   - Preserve math inline or display blocks as appropriate
4. **LaTeX Formatting Rules**:
   - Commands like $\bar{b}$, $\tilde{x}$, $\mathcal{F}$ must be inside math mode
   - Use ... for inline math,

     ...

     for display math
   - Use proper brace grouping
   - Use full Greek commands
   - Use markdown lists, not LaTeX
5. **Specific Issues Detected**:
   - Chinese characters found: 加, 叠
   - These appear to be mixed technical content and proper nouns
   - I must ensure NO Chinese characters remain
6. **Translation Rules for This Section**:
   - Author names: Romanize using pinyin
   - Journal names: Use English title if available, otherwise translate meaning
   - Institution names: Use official English names when known
   - Technical terms: Use standard English equivalents
   - DO NOT leave any Chinese characters

Let me now translate the section carefully:

2.2 Cholesterol

The text discusses cholesterol (Chol) in the context of traumatic brain injury (TBI). Key points: - Cholesterol production by astrocytes, transport via APOE, regulation by ABCA1 - 24(S)-hydroxycholesterol (24S-OHC) as main metabolite, regulated by Cyp46 and LXRs - SREBPs as cholesterol sensors - After TBI: primary injury releases cholesterol, increases free cholesterol levels - Clinical findings: increased free cholesterol in CSF - High free cholesterol causes neuroinflammation, neuronal death, BBB dysfunction, cognitive impairments - ABCA1 downregulation after TBI exacerbates pyroptosis and apoptosis - ApoE role: drops rapidly then increases to high levels by day 7 - APOE 4 allele effects: worse memory performance, related to delusions/hallucinations, affects Aβ clearance and tau deposition - 24S-OHC and Cyp46 increase after TBI, persist up to 45 days - SREBP-1 levels rise - Differential Cyp46 expression in microglia vs astrocytes - Statin use: potential benefits but requires further investigation - Atorvastatin in mouse models reduces neurological severity scores - Meta-analysis shows no significant association with GOS or mortality - Conclusion: free cholesterol accumulation and regulatory dysfunction are important mechanisms

I need to watch for any Chinese characters. I see "叠加" in the original text which means "superimposed" or "additive". I must translate this properly.

Let me go through the text sentence by sentence:

"Chol is primarily produced by astrocytes, with the vast majority being locally synthesized products transferred to neurons via lipoproteins such as apolipoprotein E (APOE)." - This is already in English, but let me check if it's part of the Chinese text. Looking at the input, it seems the section starts with some English text already. Let me re-read the input carefully.

The input text is:

```
\#\#\# 2.2 Cholesterol

Chol is primarily produced by astrocytes, with the vast majority being locally synthesized p

After TBI, primary brain injury directly destroys neurons, glial cells, and myelin structure

Regarding Chol metabolites, studies found that 24S-OHC and Cyp46 content increase significar

These results demonstrate that after TBI, free Chol content increases, metabolite 24S-OHC co
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Wait, the entire text is already in English! Let me re-read the prompt. The user says "Chinese characters found: 加, 叠" but I don't see these characters in the provided text. Let me search for them:

- "加" - I don't see this character
- "叠" - I don't see this character either

The user might have provided a pre-processed version where some parts were already translated, or the Chinese characters are embedded in a way I'm not

seeing. Let me look very carefully at the text···

Actually, I see the issue. The prompt says "These appear to be: mixed technical content and proper nouns" and mentions Chinese characters were found. But the text provided appears to be entirely in English. This is confusing.

Let me check if there are any hidden Chinese characters or if the text is actually Chinese but rendered in English. Looking at the structure, it seems like this might be a case where the user has already run some translation, or the text was originally bilingual.

Wait, I see it now! In the third paragraph, there' s a phrase: "with this 叠加 effect potentially increasing the risk" . The word "叠加" is Chinese! I missed it because it' s embedded in English text. Let me find all such instances.

Scanning the text again: - "with this 叠加 effect potentially increasing the risk" - found it!

That' s the only Chinese character instance I can find. The user mentioned "加, 叠" which are two characters, but I only see "叠加" (which contains both characters). There might be other instances I' m missing.

Let me do a more thorough scan character by character···The text seems to be predominantly English. The instruction says "DO NOT leave any Chinese characters - not even one" , so I must find and translate all of them.

Looking at the context: "with this 叠加 effect potentially increasing the risk of cognitive impairment by 3–4 times."

"叠加" means "superimposed" , "additive" , or "cumulative" . In this medical context, "additive effect" or "cumulative effect" would be appropriate.

Let me check for any other Chinese characters···I don' t see any others. The user mentioned "加, 叠" as separate characters, but they appear together as "叠加" .

Now, I need to translate this section, but it' s already mostly in English. The task is to translate the Chinese academic text, but what I' m given appears to be already translated, with just one Chinese word embedded.

Let me reconsider: Perhaps the user wants me to polish the existing English translation and ensure it' s fluent academic English, while also translating any remaining Chinese characters.

Given the instructions: - "Translate ONLY this section from Chinese to English" - "DO NOT leave any Chinese characters - not even one" - The section is "### 2.2 Cholesterol"

But the text is already in English. This suggests either: 1. The user made a mistake and provided the English version instead of Chinese 2. This is a test to see if I can identify that it' s already translated 3. There' s a subtle Chinese text I' m not seeing

Let me assume scenario 3 and look very carefully. The text starts with "### 2.2 Cholesterol" and then what appears to be English text. But maybe the original Chinese was transliterated or there's some encoding issue.

Actually, re-reading the prompt more carefully: "This is the" ### 2.2 Cholesterol" section extracted from an academic paper." and "SPECIFIC ISSUES DETECTED: - Chinese characters found: 加, 叠 - These appear to be: mixed technical content and proper nouns"

This suggests that the system has detected Chinese characters in the text, but when I look at the text, it's mostly English. The most likely explanation is that the text was originally Chinese, has been machine-translated to English, but some Chinese characters remain (like "叠加").

So my task is to: 1. Ensure the English is fluent and academic 2. Remove/translate any remaining Chinese characters 3. Follow all the formatting rules

Let me now produce a polished version of this text, fixing the "叠加" issue and ensuring the English is fluent academic prose.

The current text is: "with this 叠加 effect potentially increasing the risk of cognitive impairment by 3–4 times."

This should be: "with this additive effect potentially increasing the risk of cognitive impairment by 3–4 times."

or

"with this cumulative effect potentially increasing the risk of cognitive impairment by 3–4 times."

Given the context of genetic risk factors, "additive effect" is more appropriate.

Now, let me review the entire text for fluency and academic tone. The text is generally well-written but could use some polishing for better flow.

Let me go through paragraph by paragraph:

Paragraph 1: "Chol is primarily produced by astrocytes, with the vast majority being locally synthesized products transferred to neurons via lipoproteins such as apolipoprotein E (APOE). Its stability is regulated by the transmembrane protein ATP-binding cassette transporter A1 (ABCA1). 24(S)-hydroxycholesterol (24S-OHC) is the main metabolite of Chol in the brain, primarily regulated by cytochrome P450 family 46A1 subfamily (Cyp46) and liver X receptors (LXRs). Chol biosynthesis regulation involves cholesterol regulatory element-binding proteins and autoregulatory feedback control, particularly sterol regulatory element-binding proteins (SREBPs), which are intr### 2.3 Fatty Acids

FAs are fundamental components of most lipids and serve as energy substrates and bioactive molecules, providing approximately 20% of the brain's energy

requirements. FAs are classified by carbon bond saturation into saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). PUFA are further divided into two families based on the position of the first double bond relative to the methyl carbon: omega-3 (O3) and omega-6 (O6) PUFAs. The O3 family primarily includes α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), while the O6 family primarily includes linoleic acid (LA) and arachidonic acid (AA). DHA and AA are not only critical nutrients for neural development but also participate in synaptic plasticity and neurotransmission.

The N-acylethanolamine (NAE) family of lipid messengers has attracted significant attention. NAEs, the brain' s primary endogenous cannabinoid source, include N-palmitoylethanolamine (PEA), N-oleoylethanolamine (OEA), N-arachidonoylethanolamine (AEA), N-docosahexaenoylethanolamine (DHEA), and their oxygenated metabolites. NAEs activate G protein-coupled receptors such as cannabinoid type 1 (CB1) and type 2 (CB2) receptors, ion channels (e.g., transient receptor potential vanilloid type 1, TRPV1), and nuclear receptors in the brain and periphery, functioning as lipid messengers that play important roles in regulating inflammation, alleviating anxiety, and modulating energy metabolism disturbances.

After TBI, FAs can serve as predictive markers for TBI severity and prognosis. Medium-chain fatty acids such as octanoic acid (OA) and decanoic acid (DA) show high positive correlation with TBI severity and prognosis. After TBI, FAs exert dual roles: large amounts of oxidized free FAs generated through cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP) pathways promoting PUFA peroxidation peak at 1 hour, exacerbating neuroinflammation and oxidative stress, then gradually weaken after 4 hours, consistent with serum lipidomic profiling results in TBI patients. High free FAs stimulate increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), initiating oxidative stress that directly damages DNA, proteins, and lipids. These large quantities of inflammatory factors activate microglia and astrocytes, further destroying the BBB and leading to long-term damage and cognitive decline in TBI patients. Free FAs released by hydrolyzing PL around the injury site release DHA and AA, which instead have neurorepair-promoting effects. PL species containing DHA in the hippocampus, cortex, and plasma remain persistently decreased 3 months after injury, indicating that appropriate supplementation of beneficial FAs has therapeutic value for TBI. Studies found that DHA supplementation can promote neural repair and exert synaptic protective effects by reducing apoptosis and inflammatory responses. TBI mice fed a mixed diet of O3 and vitamin D showed improved visual function and spatial memory deficits through attenuation of persistent glial cell activation and axonal injury. A 2023 systematic review concluded that nutrients including O3 and phytocannabinoids can improve cognitive impairment, sleep disorders, anxiety, and other psychiatric symptoms after mTBI.

In summary, FAs exhibit dual pro-injury and pro-repair effects after TBI. Ox-

idized free FAs exacerbate secondary injury by inducing inflammation and oxidative stress, while consumption of endogenous protective FAs such as DHA and exogenous supplementation (e.g., O3, DHA) can improve cognitive and psychiatric symptoms through anti-inflammatory, anti-apoptotic, and neurorepair-supporting effects, providing key targets for TBI diagnosis and intervention.

The NAE family has increasingly attracted attention, with its increase after TBI considered protective, though this compensatory effect is transient and vulnerable to hydrolysis by endocannabinoid-degrading enzymes such as fatty acid amide hydrolase (FAAH), monoacylglycerol lipase, and α/β-hydrolase domain-6. Studies found that inhibiting FAAH can prolong the protective effects of NAEs, reduce neurodegeneration in the dentate gyrus, and upregulate expression of B-cell lymphoma-2 gene (Bcl-2) and heat shock protein 70 (Hsp70) in the cortex and hippocampus, thereby reducing TBI-induced behavioral deficits and neurodegeneration. Meanwhile, FAAH inhibition can significantly reduce expression of pro-inflammatory factors, α-synuclein, synaptophysin (SYP), synaptosomal-associated protein-25 (SNAP-25), and cysteine string protein α (CSPα) in the injured cortex and hippocampus, while increasing expression of amyloid precursor protein (APP) and p-Tau, greatly improving motor function and long-term or short-term memory. Research using electrophysiological detection and machine learning proposed that inhibitors targeting monoacylglycerol lipase and fatty acid amide hydrolase among endocannabinoid-degrading enzymes may be most effective in alleviating neuronal dysfunction, though further research is needed.

In summary, NAEs possess neuroprotective, synaptogenic, and anti-inflammatory properties in the nervous system but are vulnerable to hydrolysis by endocannabinoid-degrading enzymes. Investigating TBI-induced changes in endocannabinoid ligands, enzymes, and receptor molecules to fully exploit the compensatory effects of the endocannabinoid system holds important therapeutic significance and potential for TBI-induced mental disorders.

2.4 Phospholipids and Sphingomyelin

PLs are the most abundant lipid species in the brain and major components of cell membranes and mitochondrial membranes in organelles, protecting neurons and insulating nerve fibers while assisting neuronal signal transmission. Changes in their composition directly affect neural membrane permeability, leading to neurological diseases. Based on different hydrophilic residues on the phosphate group, PLs are classified into phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylglycerol (PG), and phosphatidylcholine (PC), among others. Degradation by phospholipases produces second messengers such as diacylglycerol (DAG), inositol 1,4,5-trisphosphate, lysoglycerophospholipids, and lysophosphatidylcholine (LPC), playing important roles in neuroprotection and anti-inflammation. SM is an important component of neural cell membranes, essential for maintaining brain function, particularly in neurogenesis and synaptogenesis, and has become an indispensable lipid involved in tissue damage, neuroinflammation, and resolution processes. The

core molecule in SM metabolism is ceramide (Cer), whose production and activation involve multiple pathways including the de novo pathway, sphingomyelinase (SMase) hydrolysis pathway, and salvage pathway. The salvage pathway primarily recycles sphingosine 1-phosphate (S1P), the de novo pathway depends on serine palmitoyltransferase (SPT), and the sphingomyelin hydrolysis pathway depends on SMase. Abnormal SM metabolism has been reported in various neurodegenerative and psychiatric diseases such as Alzheimer' s disease, Parkinson' s disease, and Huntington' s disease. Cardiolipin (CL), a mitochondria-specific PL, accounts for 15%–20% of all mitochondrial lipids and has recently become a research focus in neurodegenerative diseases. Abnormal CL is associated with impaired neurogenesis and neuronal dysfunction.

PL and SM can also serve as predictive markers for TBI severity. LPC and SM show strong negative correlation with TBI severity, with these lipid levels increasing significantly in mild TBI patients. Elevated SM content may indicate recruitment for myelin repair processes, while the negative correlation of LPC may be closely related to increased inflammation levels, and it has been identified as a key lipid requiring increased focus in the central nervous system after injury, suggesting that promoting absorption of these lipids is protective against injury. Experimental studies found that supplementing choline-containing PL can improve mental disorder behaviors and promote neural cell repair.

Studies found that after TBI, cell membrane damage causes massive PL hydrolysis by phospholipases, releasing large amounts of free FAs that exacerbate neuroinflammation and oxidative stress-induced mental disorders through the aforementioned pathological FA metabolic pathways. Additionally, synaptic remodeling and myelin regeneration depend on PUFA-rich PL. Since DHA-containing PL species remain persistently decreased, synaptic membrane integrity is compromised, affecting synaptic plasticity and neural signal transmission. Synaptic dysfunction directly correlates with cognitive decline and abnormal emotion regulation, representing a core mechanism of post-TBI mental disorders. Reports indicate that in the acute phase of mild TBI mice, Cer levels—the core product of SM metabolism—increase significantly in the brain, with activation pathway genes upregulated (e.g., S1P, SPT) and rate-limiting enzyme activity increased. In the chronic phase (30 days post-TBI), neutral SMase (nSMase) increases. This study indicates that acid SMase (aSMase) activates in the acute injury phase, while nSMase activates in the chronic phase. Cer possesses potent pro-inflammatory and pro-apoptotic effects, influencing TBI and neurological function through two core pathways: first, Cer can activate the nuclear factor- B (NF- B) pathway, which exacerbates intracellular effects of inflammatory cytokines and promotes release of pro-inflammatory factors such as IL-6 and TNF-α, amplifying neuroinflammatory responses. Second, Cer can directly induce neuronal apoptosis, causing neuronal damage in the hippocampus and prefrontal cortex, which ultimately leads to functional abnormalities commonly seen after TBI such as cognitive decline and mood disorders. Previous reports state that the aSMase-Cer pathway plays a key role in major depressive disorder triggered by TBI. Studies show that intraperitoneal injection of the aSMase

inhibitor imipramine (10 mg/kg) in TBI rats significantly reduced Cer levels, markedly decreased dendritic spine loss, improved cognitive dysfunction, and reduced neurological scores. Currently, clinical studies targeting the aSMase-Cer pathway in TBI have not been widely conducted, though significant efficacy in basic research has provided direction for future clinical studies. Multi-center clinical trials are needed to verify its safety and effectiveness and provide new strategies for improving patient prognosis.

CL has recently become a hotspot in degenerative diseases. Starting 3 hours after TBI, cytochrome complex (Cytc) and CL complexes interact to generate hundreds of unique oxidized CL species. Altered distribution of oxidized CL regulates pro-apoptotic mitochondrial permeability changes and cytoplasmic Cytc release. After experimental TBI, oxidized CL hydrolysis produces large amounts of inflammatory mediators that regulate pro-inflammatory and anti-inflammatory responses, indicating that targeting CL oxidation/hydrolysis as a therapeutic target for TBI has potential significance. Researchers found that using mitochondria-targeted electron scavengers can prevent CL oxidation, reducing neuronal death, lesion volume, and behavioral deficits in both in vivo and in vitro models. However, some studies found that TBI-induced mitophagy is a CL-dominated endogenous neuroprotective process that eliminates damaged mitochondria, thereby limiting neuronal death and behavioral deficits. Additionally, plasma CL content after TBI can serve as an early marker for TBI severity and treatment response, holding certain potential value, though CL' s role in TBI remains incompletely understood and requires further exploration.

In summary, PL and SM participate in TBI pathophysiological processes through structural maintenance, signal transduction, and metabolic regulation. Their level changes can serve as predictive markers for TBI severity, and metabolic disturbances (e.g., PL hydrolysis, aSMase-Cer) are key mechanisms triggering neuroinflammation, synaptic dysfunction, and mental disorders. A series of preclinical studies have confirmed the potential value of targeting PL and SM metabolism, but relevant clinical studies have not been widely conducted. Future multi-center clinical trials are needed to verify safety and effectiveness and provide new strategies for improving TBI prognosis. Mitochondria-specific CL oxidation after TBI directly involves triggering and execution of apoptosis, producing large amounts of inflammatory mediators that exacerbate TBI damage. However, CL can also exert certain neuroprotective effects by mediating damaged mitochondrial autophagy. Therefore, studying various pathological effector pathways after CL oxidation is highly meaningful for TBI treatment.

3.1 Physiological Acid-Base Balance

Intracellular and extracellular pH homeostasis is crucial for internal stability, with its balanced state directly affecting cell function through interactions between intra/extravascular and interstitial compartments. In the cranium, cerebrospinal fluid pH (CSF pH) plays a key regulatory role in ventilation control and cerebral blood flow (CBF). Specifically, CO2 transport across vascular walls

depends on arterial partial pressure of CO2 (PaCO2)-mediated cerebrovascular responses. PaCO2 changes the pH of perivascular extracellular fluid, thereby affecting cerebrovascular status. Early studies found that CBF increases 2.5-fold for every 0.1 unit decrease in CSF pH. Furthermore, when PaCO2 changes, CSF [H+]/PCO2 adjusts rapidly within seconds, while changes in CSF [HCO3-] are relatively slow. This difference in speed can alleviate drastic pH fluctuations in brain extracellular fluid, providing buffering regulation. In summary, the combined effects of arterial and extravascular/interstitial pH, PaCO2, and HCO3- jointly regulate cranial acid-base balance and cerebrovascular regulatory function.

3.2 Acid-Base Imbalance After TBI

After acute TBI, patients' average brain tissue PaCO2 increases significantly, reaching maximum values at 6 hours. Increased PaCO2 directly correlates with poor brain tissue oxygenation and positively correlates with prognosis. Brain tissue pH shows significant negative correlation with brain tissue PaCO2. The average brain tissue pH in acute TBI patients significantly decreases on day 1 post-injury. Through the Na+/H+ antiporter system and passive Cl-/HCO3- influx, brain tissue acidosis exacerbates cerebral edema. Notably, acidosis may directly promote opening of mitochondrial permeability transition pores, displacing calcium ions from their protein binding sites, interfering with mitochondrial ATP production, leading to insufficient neuronal energy supply, affecting synaptic transmission and repair functions. Increased free Ca2+ levels exacerbate mitochondrial metabolic damage, while Ca2+ triggers calpain to hydrolyze axonal cytoskeletal proteins, causing irreversible axonal damage. Additionally, brain tissue acidosis enhances N-methyl-D-aspartate receptor (NMDAR) activity, promotes glutamate release, generates toxic levels of nitric oxide (NO), triggers excitotoxic reactions, and induces neuronal apoptosis. Acid-base imbalance can also stimulate microglial activation, releasing pro-inflammatory factors that trigger neuroinflammatory cascades, further destroying neural circuits. Importantly, acid-base imbalance directly promotes cerebral edema through abnormal ion transport. Studies found that over 20% of TBI patients show significantly elevated K+ levels in dialysate, with corresponding increases in glutamate and lactate. Glutamate-induced ion flux increases may worsen intracranial pressure and cerebral edema, indicating that elevated K+ in dialysate strongly correlates with increased cerebral edema and poor prognosis. After severe TBI, brain tissue lactate levels increase significantly, with secondary hypoxia further elevating brain tissue lactate levels. Long-term brain tissue lactate accumulation may also cause mitochondrial abnormalities and inhibit normal oxidative metabolism. Regarding lactate treatment, studies show that increasing PaO2 of saturated hemoglobin in the early injury phase can reduce brain tissue lactate levels, but this treatment has drawbacks as it cannot balance glucose oxidation in glucose metabolism and may exacerbate glucose metabolism disturbances, exerting negative effects.

Clinically, using 8.4% NaHCO3 in acute TBI patients can significantly reduce

intracranial pressure and cerebral edema. A 2018 systematic review similarly found that NaHCO3 solution can indeed reduce intracranial pressure and cerebral edema without accompanying PaCO2 elevation, though it lacks higher-quality data support due to small sample sizes. To correct secondary effects of intracranial pressure, administering 30 g/L sodium chloride to TBI patients is currently a more recognized treatment, but it may cause hyperchloremic acidosis. A newly proposed treatment is intravenous hypertonic lactate, which not only increases glucose availability, reduces intracranial pressure, and improves cognition, but also maintains systemic chloride balance, though it similarly lacks large-sample data support. Emerging treatments also include targeting voltage-gated proton channel Hv1 to reduce acid-base imbalance at its source, but this remains in preclinical research.

In summary, after TBI, brain tissue PaCO2 increases significantly, pH decreases, Na+/H+ antiporter system and passive Cl-/HCO3- influx increase Na+, Cl-, and HCO3- influx, causing brain tissue acidosis that exacerbates cerebral edema and mitochondrial metabolic damage. Elevated K+, glutamate, and lactate in dialysate also worsen intracranial pressure and cerebral edema, triggering mitochondrial dysfunction, excitotoxicity, and neuroinflammation, forming a vicious injury cycle. Clinically, intravenous NaHCO3 and 30 g/L sodium chloride can both reduce intracranial pressure but suffer from insufficient evidence and adverse reactions, while emerging therapies such as intravenous hypertonic lactate and targeting Hv1 proton channels lack more data support. Correcting acid-base imbalance is a critical link in TBI treatment, and its significance for improvement cannot be underestimated, requiring further exploratory research.

A comparison of metabolism in normal physiological and post-TBI pathological states is shown in Table 1 .

4 Summary and Outlook

Metabolic homeostasis primarily includes glucose, lipid, and acid-base balance, playing crucial roles in biological growth, development, and homeostasis maintenance. Metabolic disorders after TBI are one of the core mechanisms of secondary brain injury and mental disorder occurrence. The three major disturbances—glucose metabolism, lipid metabolism, and acid-base imbalance—intertwine and collectively drive injury progression. After TBI, glucose metabolism disorder manifests as reduced brain glucose metabolism, glucose supply-demand imbalance caused by stress hyperglycemia, accompanied by abnormal insulin signaling that interacts with neuroinflammation, oxidative stress, and other mechanisms to exacerbate neuronal deficits. Lipid metabolism disorder manifests as free Chol accumulation, dual FA effects (oxidized free FAs are pro-inflammatory while protective FAs like DHA promote repair), PL metabolic disturbance (CL oxidation involves triggering and execution of apoptosis), and SM metabolic disturbance (Cer is pro-inflammatory and pro-apoptotic). Interventions targeting lipid metabolism disorders show great potential, but clinical evidence still needs strengthening. Acid-base imbalance, through abnormal ion transport after TBI, causes tissue acidosis that induces excitotoxicity and exacerbates cerebral edema

and intracranial hypertension. Therapeutic measures similarly suffer from insufficient evidence strength and require further exploratory research.

Acid-base imbalance does not exist in isolation in TBI pathological processes but rather forms a "vicious cycle" with inflammation, excitotoxicity, and cerebral edema. Correcting acid-base imbalance is an important component of comprehensive TBI management, and its significance for improving psychiatric symptoms cannot be underestimated. Current research has basically clarified the core role of the three major metabolic disturbances in TBI and some key mechanisms, but limitations remain. First, intervention methods are mostly based on single metabolic targets, lacking regulatory effects on the overall metabolic network. Second, clinical evidence mostly comes from small-sample studies, with large-scale validation still lacking. Future research should focus on three aspects: first, clarifying the cross-regulatory network among the three major metabolisms and analyzing the weight of each metabolic pathway in different injury stages; second, developing personalized targeted treatment strategies, such as combining biomarker changes to screen sensitive populations, optimizing drug intervention doses and timing, and conducting personalized treatments; third, promoting clinical translation of drugs through large-scale trials to verify the safety and stability of emerging therapies. Combining these three approaches will ultimately achieve synergistic intervention for metabolic disorders after TBI, providing more favorable help for improving mental function and prognosis in TBI patients.

Author contributions: DING Jiameng was responsible for conceptualizing the article, collecting and organizing research materials, and drafting the manuscript. LI Xiong was responsible for quality control and research material collection. MA Xiao and CHENG Hao were responsible for table preparation and article quality control. YAN He and ZHANG Dongxian were responsible for final revision and critical review of the paper.

Conflicts of interest: None declared.

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