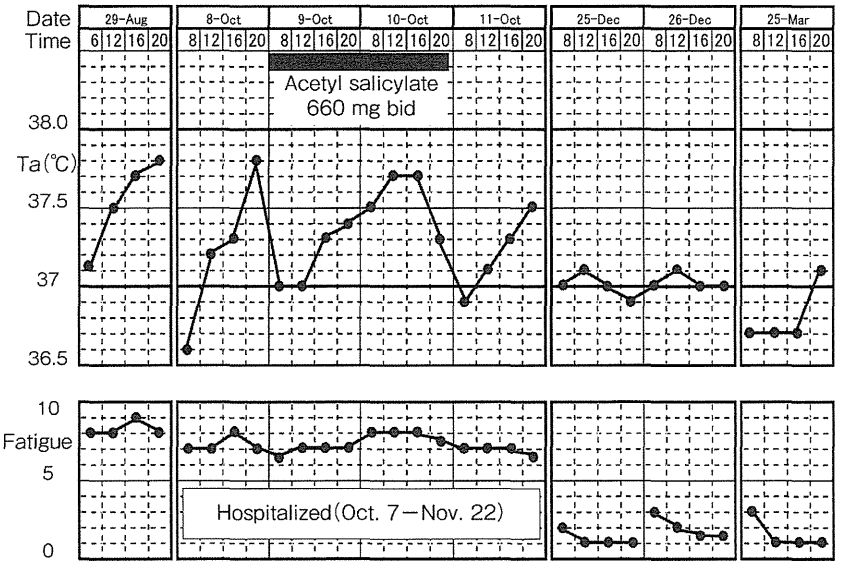

Fig. 5　慢性疲労症候群症例 2 の微熱と倦怠感の経過
10 月 9 日，10 日に acetyl salicylic acid 660 mg を内服したが体温は低下しなかった．倦怠感の強さは，ないときを 0，最もつらいときを 10 としたときの numerical rating scale で示した．Ta：腋窩温．文献 8 より引用

しながら，この患者のような顕著なものではない．例えば 26～33 歳のレジデントの医師が試験を受ける直前の腋窩温は，2，3 週間後の同じ時間帯の腋窩温より 0.6℃高い 37.0℃であった[9]．18～27 歳の学生が試験を受ける直前の口腔温は，試験終了 3 日後の同じ時間帯の温度より 0.18℃高い 37.4℃であった[10]という報告がある．ところが症例 2（26 歳，女性）では，1 時間の面接で 38.2℃まで腋窩温が上昇した．動物実験では，繰り返しストレスは急性 SIH の程度を増大させることが示されている．例えば，繰り返し拘束ストレスを受けた後のラットでは，コントロールラットに比べて，ノルアドレナリン誘発性の核心温上昇，褐色脂肪組織の温度上昇，酸素消費量の増大反応が顕著であった[6]．この結果は，繰り返しストレスに曝露されると，交感神経性産熱反応が増大することを示している．したがって CFS 患者の中には，発症に先行する慢性ストレスによって，患者が情動的な出来事に曝露されたとき，健常人よりも顕著な高体温反応を生じる者がいるのだろう．

3．CFS 患者にみられる微熱の治療

Fig. 5 に，症例 2 の治療経過を記した．患者は 9 月，当科を紹介されて受診した．受診時にはすでに休職して自宅療養中であった．補中益気湯，trazodone などによる薬物療法が行われたが，病状は改善しないため，10 月 7 日，入院となった．文献 11 に記したストレス対処行動に関する質問紙から，患者は疲労を感じたときに，疲れに負けてはいけない，と自分を励ましたり，いくら疲れても最後までやりとげようと，自らを鼓舞するという対処行動をとるために，適切な休息行動がとれていないことがわかった．また，「忙しくしていないと不安だ，いやなことを考えてしまいそうだ，忘れたいことがあるのでわざと忙しくする」と答えるなど，回避の手段として，わざと忙しくしていることがわかった．入院後の面接で，これらの行動様式は，完璧な看護師である母親から，褒められたことがない（そのため愛してもらっていると感じたことがない）ことに由来する自尊心の低さと，認められたいための過剰な努力に由来することが

わかった．

入院治療は文献11のプロトコールに基づいて行った．つまり，入院時，十分な安静，休養を促すために，面会，通信を禁止し，テレビやラジオの視聴，読書を制限することと，その意味を説明した．そして「不安に感じたとき，疑問をもったとき，つらいことを思い出したとき，誰かに話を聞いてほしいときには，遠慮なく医療スタッフに話してください．泣きたくなったときに泣くことも大切な治療です」と，患者の気兼ねを最小限にし，抑圧感情を吐露しやすい下地を作るための働きかけを行った．また治療スタッフ全員で，この質問項目の答えを共有し，患者の低い自尊心に対しては，医療者の態度が温かい（と患者が感じる）ものになるよう配慮し，患者自身が，ありのままの自分を受け入れ，認めることができやすいような働きかけを行うことで統一した．

患者に対しては，入院中に取り組む課題をシートにして渡した．①食事をするときは，味わいながら，ゆっくりと食べてください，②散歩するときには，景色を楽しみながらゆっくり歩いてください，③脳疲労のサインを理解し，脳が疲れたらこまめに休息してください，④脳のアイドリング状態に気づいて，気づいたら，気持ちが整う状態に戻しましょう，などである．特に①②は，この患者のように，がむしゃらに頑張って体調を崩した患者には重要で，ゆったりすることによって，世界が変わってみえること，疲れを忘れようとしてきたことによって抑制されていた，本来の身体感覚がよみがえってくること，それが克服すべき不安を惹起すべきものではなく，心地よいものであることを体験してもらうと同時に，それを習慣化してもらうためである．外部刺激を制限すると，頭の中で反芻している問題がクローズアップしてくるので，疲労がある程度改善した段階で，不要な反芻を解決するために，担当医が定期的に面接すると同時に，「整える療法」を行ってもらう．緊張の強い患者に対しては自律訓練法を指導する．つまり，入院期間中に行う治療としては，刺激統制，治療スタッフの対応についての取り決めなどを含む治療の枠組み作り，薬物療法，心理療法（適応的でない認知や行動の修正，抑制していた感情表出の受容など），段階的な運動療法（散歩），整える療法や自律訓練法の指導などが挙げられる．この症例のようなCFS患者に対する心理療法は，他の疾患患者に比べて2つの点で難しい．第一点目は，疲労，集中力低下が著しい疾患である点にある．心理療法という治療が患者を疲弊させてはいけない．第二点目は，失感情，失体感傾向の強い者が多い点である．このような患者に対しては言語的心理療法が難しいことが多い．積極的な心理療法を導入する前に，筆者は①〜④を指導するようにしている．

以上の複数の治療を，患者の疲労を増悪させることなく，段階に応じて，短期間で行う必要がある．そのため筆者は，微熱を伴うCFS患者の入院治療をプロトコール化しており，患者に対しても治療段階に応じて，取り組むべきこと，注意点について書いたシートを配布することで，研修医でも一定の治療ができるよう，工夫している．

このような治療を行うと，これまで疲れを感じないようにすることで社会適応してきた患者は，どっと疲れを感じるようになり，最初の1週間は疲労感が増悪した．しかし，その後は，**Fig. 5**のように，微熱，疲労感ともに改善した．本症例では，あわせてTAS-20得点は66点から51点に，失体感症尺度[12]は73点から61点に低下し，失感情症，失体感症の状態も改善した．

まとめ

今回紹介した症例のように，CFS患者の中には，微熱の発症，増悪に心理社会的ストレスが関与する症例が存在する．CFS患者における顕著なストレス性体温上昇反応は，発症前に慢性

的なストレス状態が存在する症例に多い．したがって，本稿の中で紹介した治療は，ウイルス感染を疑わせる患者よりも，ストレスの関与の大きいCFS患者に対してより有効な治療法と考えられる．

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Abstract

Psychological Stress Contributes to the Development of Low-grade Fever in Chronic Fatigue Syndrome Patients

Takakazu Oka*

*Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University
(*Mailing Address*：Takakazu Oka, 3-1-1 Maidashi, Higashi-ku, Fukuoka-shi, Fukuoka 812-8582, Japan)

Low-grade fever is a common symptom in patients with chronic fatigue syndrome (CFS). The mechanisms responsible for its development are poorly understood. However, several phenomena suggest that psychological stress contributes to the development and exacerbation of low-grade fever in some CFS patients. One phenomenon is workday hyperthermia. Here some patients exhibit higher axillary temperatures on working days compared with holidays. Another phenomenon is a robust stress-induced hyperthermic response. That is, some patients develop extremely high core temperatures (e. g., up to 1.0°C increase within one hour) during psychological stress-associated interview.

This article reviews how psychological stress affect the body temperature in CFS patients and describes the treatment of CFS patients whose low-grade fever is associated with psychological stress.

Key words：stress, chronic fatigue syndrome, psychogenic fever, stress-induced hyperthermia, fever of unknown origin

日本心身医学会会員の皆さまへ

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第5章　心身症の治療

ヨガ・気功

要旨

ヨガや気功は，ストレスによって生じる精神，神経，免疫，内分泌的変化に対して拮抗的な作用を発揮する．そのため，ヨガや気功は健康な人のストレス管理の一環，さらにストレス性疾患の治療法として効果が期待できる．しかしながら，その効果は限定的であるため，現代医学的治療に付加する形で用いるべきである．また，患者がヨガや気功を練習する場合，担当医はその指導者と緊密に連携することが重要である．

●キーワード

ヨガ
気功
瞑想的運動療法
心身症
ストレス

はじめに

ヨガや気功は，健康な人のストレスマネジメントの一環としてだけでなく，心身症を始めとするストレス関連疾患の治療法として，広く用いることができる．最近は，奏効機序に関する基礎研究だけでなく，臨床効果に関する無作為化比較対照試験（RCT）も増えてきている．ヨガと気功は奏効機序，医学的効果，そして治療法としての位置付けが似ているため，本稿ではヨガを中心に解説する．

医療としてのヨガ

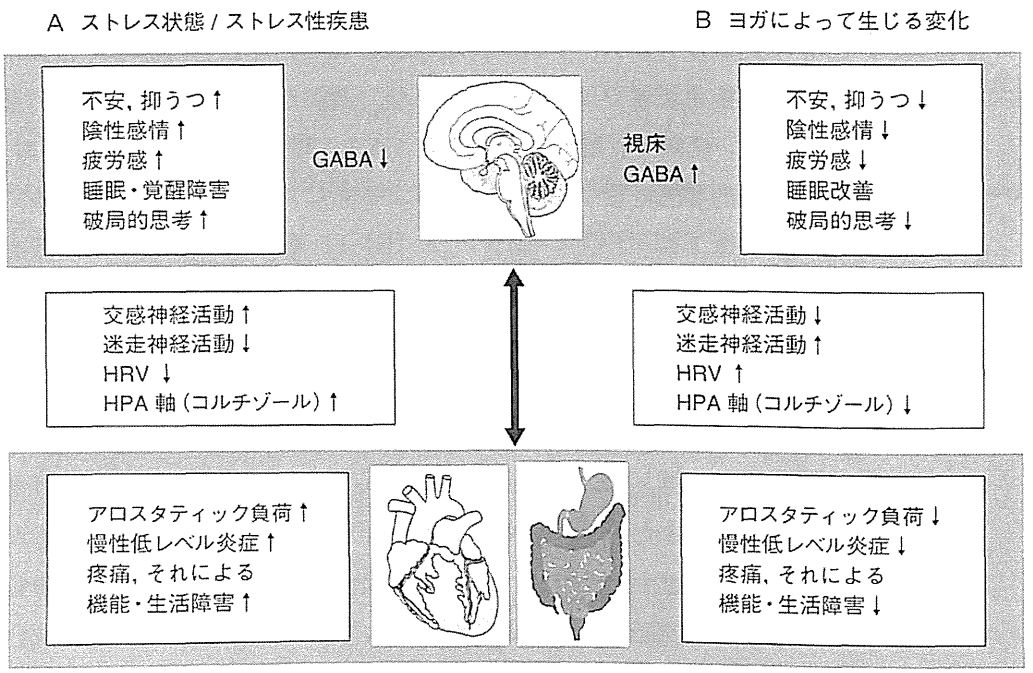
ヨガの教典である『ヨガ・スートラ』によると，ヨガとは心の作用の抑制である．それは本来，解脱を達成するために必要なものであるが，具体的な方法論として8つの段階が説かれている．この中で，医療として用いられ，また研究されているのは，主にアーサナ（体位法），プラナヤーマ（呼吸法），瞑想法の3つ，もしくはそれらを組み合わせたものが多い．

ヨガによって生じる心理的身体的変化

健康な人がストレスフルな状況におかれたとき，もしくはストレス関連疾患患者では，不安，抑うつ，落胆などの陰性感情，疲労感が増加し，睡眠・覚醒障害が生じる．また，疼痛などの身体症状に対して，破局的な思考をするようになる．さらに，交感神経・副腎髄質系および視床下部-下垂体-副腎皮質（HPA）系の活動が亢進し，迷走神経活動が抑制される．心拍変動（HRV）も低下する．これらの神経・内分泌的変化は，短期的にはストレスに対する適応反応であっても，長期的にはC反応性タンパク（CRP）やインターロイキン-6（interleukin-6：IL-6）などを増加させ，慢性低レベルの炎症が持続，増悪する結果となる．アロスタティック負荷（ストレスフルな外部環境に適応するためのエネルギーの消耗）の状態となり，さまざまな身体疾患が増悪する．特に，痛みが増強すると，それによる機能障害，生活障害も問題となる（図1）．ヨガを練習すると，これらの変化に対して拮抗的な反応が生じる．必ずしもすべての研究結果が一致するわけではないが，ヨガはおおむね，不安，抑うつ，陰性感情，疲労感を減少させ，痛みに対する破局的思考や睡眠障害を改善する．交感神経活動と血中，唾液中コルチゾール値を低下させ，HRVを増加させる．血中CRPやIL-6などの炎症マーカーの値が低下，もしくはストレス性に生じる増加が抑制される[1]．筋骨格系の痛みと，それによる機能・生活障害が改善される．

近年，ヨガアーサナを1時間行うと脳内でγ-アミノ酪酸（GABA）が増加することが明らかにされた[2]．GABAは鎮静，抗痙攣，抗不安作用を持つ抑制性神経伝達物質である．脳内GABA系の低下に加え，ストレス性に増悪する，HRVが低値となる，などの共通点を持つ疾患に，てんかん，大うつ病，心的外傷後ストレス障害（PTSD），慢性疼痛などがある．ヨガがストレス関連疾患，特にてんかん，不安障害，大うつ病，慢性疼痛に対して有用性を発揮する機序の1つとして，HRVと脳内GABAの増加が示唆されている[3]．

図1　ヨガのストレス性疾患に対する奏効機序



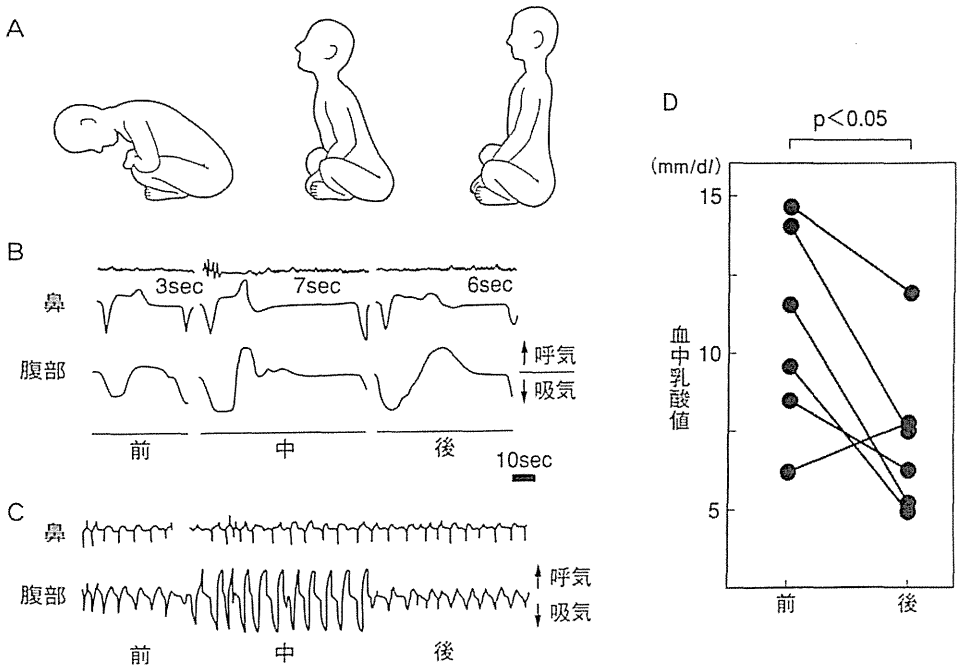
健康な人のストレス状態，もしくはストレス性疾患患者で見られる病態（A）に対して，ヨガは拮抗的に作用することが分かる（B）．

HRV：心拍変動，HPA：視床下部-下垂体-副腎皮質（系），GABA：γ-アミノ酪酸

ヨガの臨床効果に関するエビデンス

ヨガに関する RCT，システマティックレビュー，メタアナリシスも増えてきた[4~6]．ヨガはうつ病，PTSD，てんかん，統合失調症，注意欠陥・多動性障害などの精神疾患，がん患者，多発性硬化症，線維筋痛症などの身体疾患患者の訴える疲労感や精神的愁訴，筋骨格系（骨関節炎，リウマチ，中等～重度の腰痛症）の慢性疼痛に対して有効であるとする RCT がある．特に，腰痛に対しては，ヨガは通常治療群と比較して医療費を抑制できたとする報告がある[7]．

図2 ヨガアーサナは呼吸を深くし，血中乳酸値を低下させる（文献[8)10)]より引用改変）



合蹠前屈のポーズ（A）を行なうと，呼吸は自然に深く，長く，呼気の延長した（B）腹式呼吸となり，ポーズ終了後も規則正しい状態が持続する（C）ことが分かる[8)]．気管支喘息患者がヨガアーサナを1時間練習すると血中乳酸値は低下した（D）[10)]．

ストレス関連疾患，心身症に対する臨床経験

筆者はこれまで，心因の関与する気管支喘息[8~10)]，痙性斜頸[11)]，難治性胃潰瘍[12)]，慢性疲労症候群患者に対してヨガを指導し，有用性を実感している．気管支喘息患者では，約1時間のヨガ（アーサナ，プラナヤーマ）は，肺機能を増悪させたり運動誘発性喘息発作を生じることなく，呼吸困難感を改善した．この改善効果は，肺機能の悪い者でより顕著であった．ヨガアーサナによって，呼吸筋疲労が改善するためではないかと考えられる．痙性斜頸患者では，呼気優位のゆっくりした呼吸とともに両上肢をゆっくり挙上するという練習により，胸鎖乳突筋の表面筋電位が低下し，斜頸が改善した．失体感症傾向の強い胃潰瘍患者では，図2に示したヨガを行うことで，初めてリラックスした感覚をつかむことができ，普段の自分がいかに緊張していたか，

リラックスすると胃痛が軽減することなど，言語的心理療法では難しかった心身相関の洞察が促され，潰瘍が瘢痕治癒した．

したがって，浅い不規則な呼吸パターン，呼吸筋疲労が症状形成に関与している患者や，失体感症傾向の強い心身症患者に対して，ヨガは特に試みる価値がある．

治療法としてヨガを導入する際の注意点

ヨガアーサナ（ヨガのポーズ）では，日常動作ではあまり用いない筋肉を使った動作を行い，目的の姿勢（ポーズの完成形）を一定時間，保持する．そのため，アーサナはストレッチ，アイソメトリック運動の要素を含み，ポーズを完成させるためには，ある程度の柔軟性と筋力が求められる．したがって，筋骨格系疾患患者がヨガを行う場合，無理なストレッチ，無理な方向の動作を行うと，痛みが増す危険性がある．実際，慢性疼痛に対して有効であるとする RCT 研究でも，ヨガによってかえって痛みが増した者や，ヨガを導入後，ドロップアウトした者が一定の割合で存在する．疼痛性疾患患者がヨガを行う場合，医療者はヨガ指導者と緊密に連携をとり，痛みを増悪させないよう，ポーズを限定，工夫すべきである．また完全癖が強く，それが病態と関連している患者では，アーサナを正確に，完全に行なおうとするあまり，かえって緊張状態を増悪させる場合がある．このような患者の場合，患者がポーズによってリラックスできるように，指導を工夫する必要がある．さらに高血圧，動脈硬化の強い患者においては，逆立ちや頸部の強い屈曲，伸展を伴う動作は避けるほうが良い．精神疾患患者の中で，過去に外傷体験がある者の中には，目を閉じてポーズを行うことに強い恐怖を感じたり，ポーズを直すためにヨガ指導者が患者の背後に回ったり身体的に接触すると，外傷体験を再体験する場合がある．医療者はヨガ指導者に対して，あらかじめ可能な範囲内で病状を説明しておき，このようなことが起らないよう配慮すべきである．

医療の中でのヨガの位置付け

ヨガによって生じる精神・身体的変化は，心身症，ストレス性疾患の予防，治療として好ましいものである．しかしながら，この変化量が臨床効果をもたらすに十分なものかという点については必ずしも明

らかではなく，またヨガ単独による治療が，現代医学的治療より優れているかどうかを検討した報告は限られている．

したがって現時点では，ヨガをストレス関連疾患，身体疾患の治療法として用いるときには，現代医学的治療のアドオンセラピーとして，現代医学に基づく医療に付け加える形で用いるのが良い，と考えられる．

今後の問題点

1．研究の問題点

これまでの研究で用いられているヨガの内容は，決して均質なものではない．最初に述べたとおり，アーサナとプラナヤーマを用いたプログラムの有効性を検討した研究が多いが，用いたポーズはそれぞれ異なっている．また現時点では，ヨガが臨床効果を挙げるために必要な用量設定，つまり，臨床的に意義のある変化を得るためにはヨガを1日何分，週に何回，何週以上行う必要があるのか，が明らかではない．今後，共通のプログラムを用いた，一層，質の高い臨床研究が必要である．

2．医療者-ヨガ指導者連携

現在，我が国にはヨガを指導する人的資源は豊富に存在し，国民の多くが，健康増進のためにヨガを活用している．医療機関にかかりながら，ヨガ教室に定期的に通っている患者も少なくない．心身症，ストレス性疾患の治療として現在医学的治療とヨガを併用する場合には，医療者とヨガ指導者が密接に連携することが望ましい．

注：最初に述べたように，気功，太極拳の医学的効能，機序はヨガと共通する部分が多い．そのため，ヨガ，気功，太極拳を，瞑想的運動療法（meditative movement therapy）と総称して考える研究者もいる．

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Influence of Psychological Stress on Chronic Fatigue Syndrome

Takakazu Oka*
Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan

Abstract. This article reviews the influence of psychological stress on chronic fatigue syndrome (CFS). Studies have demonstrated that psychological stress is involved in the CFS onset, exacerbation, and/or relapse, while early life stress acts as a risk factor toward the development of CFS in later life. CFS patients may have disrupted stress systems, including HPA axis hypofunction and ANS alterations characterized by sympathetic overactivity and low vagal tone. Individuals with CFS respond to psychological stress differently from healthy subjects in that CFS patients show a blunted (or similar) activation of the HPA axis and SNS and attenuation of proinflammatory cytokine induction, whereas psychological stress increases cytokine levels in healthy subjects. It is not fully understood how such disrupted stress systems and differential stress responsiveness contribute to the pathophysiology of CFS. Further studies are necessary to determine whether laboratory stress can fully replicate typical daily stress and how stress responsiveness is related to psychological stress-induced exacerbation of CFS symptoms. This article also reviews the role of psychological stress in low-grade fever in CFS and the role of adaptive or maladaptive coping in the severity of CFS symptoms.

Keywords: Chronic fatigue syndrome, psychological stress, stress-induced hyperthermia

INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing debilitating fatigue for at least 6 months. The fatigue is accompanied by specific symptoms, such as impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, joint pain, headaches, unrefreshing sleep, post-exertion malaise [1], and low-grade fever [2].

The pathophysiological mechanisms underlying CFS are still poorly understood. However, recent studies suggest that psychological stress is associated with the onset, exacerbation, or recurrence of CFS and also acts as a risk factor for developing CFS. Psychological stress is mainly relayed from the brain to the body via two major pathways, i.e., the hypothalamic-pituitary-adrenal (HPA) axis with the resultant release of cortisol and the sympathetic nervous system (SNS) with the resultant release of catecholamines (noradrenaline and adrenaline), with both pathways affecting the immune system [3]. This article reviews the characteristics of the stress systems of CFS patients and how psychological stress affects these systems. It also discusses possible mechanisms by which psychological stress influences CFS.

*Correspondence to: Dr. Takakazu Oka, Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel.: +81 092 642 5317; Fax: +81 092 642 5336; E-mail: oka-t@cephal.med.kyushu-u.ac.jp.

STRESS SYSTEMS OF CFS PATIENTS

Neuroendocrine systems such as the HPA axis and the autonomic nervous system (ANS), particularly the SNS, are key regulatory systems for organisms to cope with stressors and to adapt to environmental changes.

In CFS patients, a dysfunction of the HPA axis is hypothesized. Such dysfunction includes a reduced 24-hour urinary free cortisol, attenuated evening plasma cortisol levels, reduced cortisol responses to adrenocorticotropic hormone (ACTH) administration, and/or blunted ACTH responses to oral corticotropin-releasing hormone (CRH) in CFS patients versus control subjects [4–6]. Although there are contradictory reports [7–10], a recent meta-analysis revealed

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that the cortisol awakening response (CAR), a surge of cortisol levels upon awakening, is attenuated in CFS patients compared to control subjects [11–13]. This suggests that an attenuation of cortisol diurnal variability, not total cortisol output, is important in relation to fatigue in CFS. In CFS patients, an autonomic dysfunction is also suggested. For example, CFS patients have a higher heart rate (HR) and higher plasma levels of adrenaline or noradrenaline versus healthy subjects at rest and even during sleep [14–17], whereas cardiac vagal tone is lower compared to healthy subjects [18, 19]. These findings suggest a sympathetic ANS predominance in CFS patients. Furthermore, at least some CFS patients may have an immunologic dysfunction [20–23], which includes a slight increase in proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) [24, 25] along with other inflammatory parameters such as nuclear factor-κB (NF-κB) [26] or C-reactive protein [27]. Thus, HPA axis hypofunction, ANS alterations characterized by sympathetic overactivity and low vagal tone, and immune abnormalities may play a role in CFS.

INFLUENCE OF PSYCHOLOGICAL STRESS ON CFS

Several lines of evidence suggest that psychological stress influences CFS. First, childhood trauma is demonstrated to be an important risk factor for CFS [28]. Such trauma includes sexual, physical, and emotional abuse as well as emotional and physical neglect. Exposure to such trauma was associated with a 3 – 8-fold increased risk for CFS [28, 29]. Furthermore, experience of childhood trauma is associated with greater CFS symptom severity in later life [28]. As individuals with CFS who had experienced childhood trauma, but not those with CFS without trauma, had an attenuated CAR compared to controls, early life trauma may lead to dysregulated stress systems in CFS [29].

Secondly, development of CFS is often predated by stressful life events [30–32]. Several studies have demonstrated that negative life events are related to CFS onset [31, 32], exacerbation, and relapse [30], whereas positive life events may contribute to the process of recovery after the establishment of CFS (Fig. 1) [33].

EFFECTS OF LABORATORY PSYCHOLOGICAL STRESS ON STRESS AND IMMUNE SYSTEMS IN CFS PATIENTS

If psychological stress is related to CFS vulnerability, development, exacerbation and/or relapse, psychological stress may lead to CFS symptoms via affecting stress systems. So far, however, studies are limited on how psychological stress in daily life affects

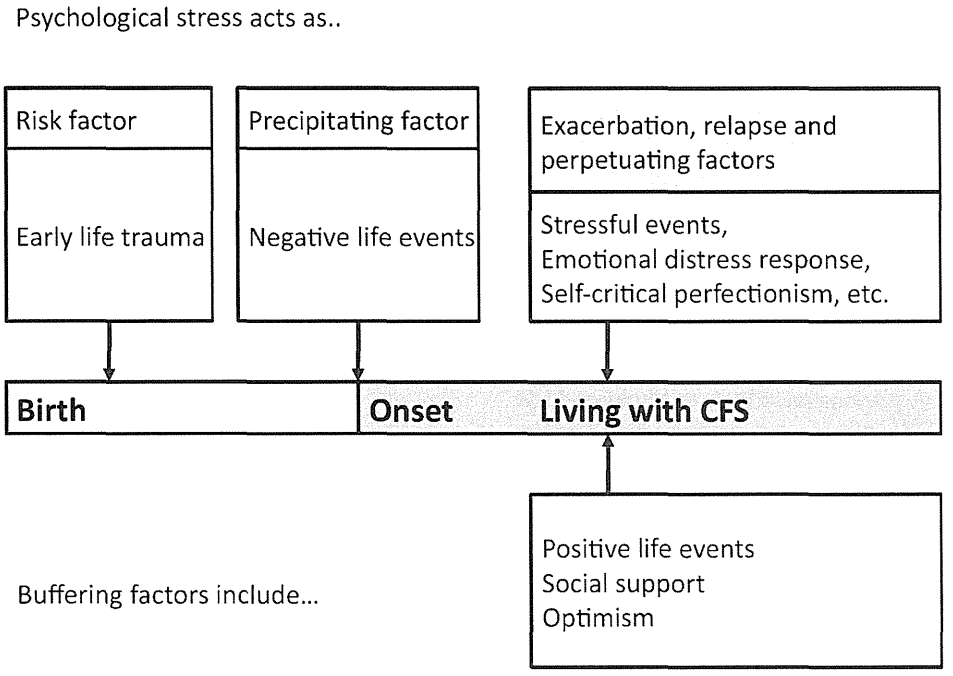

Fig. 1. Possible influences of psychological stress on CFS.

Table 1
Characteristics of neuroendocrine, autonomic, and immune systems at rest and following experimental stress in CFS patients when compared with healthy subjects

(a) Basal	(b) Response to acute psychological stress
HPA axis: Hypofunction	HPA axis: Weaker ACTH increase. Similar cortisol increase vs. healthy subjects
ANS: Sympathetic overactivity. Low vagal tone	ANS: Weaker or similar HR increase. Similar BP increase vs. healthy subjects
Immune: Pro-inflammatory. Increase in proinflammatory cytokines and inflammatory parameters	Immune: Suppression of cytokine production (cf. in healthy subjects, increase in cytokine production)

CFS patients. Therefore, for a greater understanding of this interaction, I summarized the effects of laboratory psychological stress on neuroendocrine, autonomic, and immune functions in CFS patients and healthy subjects in Table 1. Considering the stress system characteristics and enhanced inflammation in CFS patients, it is possible to hypothesize that psychological stress may induce insufficient HPA axis activation, greater sympathetic nervous system responses, and more production of proinflammatory cytokines in CFS patients when compared to healthy subjects, which may lead to an exacerbation of CFS symptoms.

Indeed, laboratory psychological stress increases the number and severity of psychological as well as physical symptoms in CFS patients [34], suggesting that psychological stress exacerbates CFS features. However, although stress-induced increases in plasma ACTH in CFS patients were blunted compared to control subjects, the increases in plasma cortisol and salivary free cortisol in CFS patients were not different from healthy subjects [35, 36]. Stress-induced cardiovascular changes in CFS patients were also not different from healthy subjects [35, 37]. Rather, several studies have demonstrated that stress-induced HR responses in CFS patients were weaker versus healthy subjects [38, 39]. One study suggests that patients with the lowest cardiovascular reactivity to stress had the highest rating of CFS symptom severity [39]. In healthy subjects, psychological stress increased LPS-induced IL-6 and TNF-α levels. However, in CFS patients, psychological stress decreased levels of both cytokines [36, 40].

These studies suggest that, in healthy subjects, short-term (several min – 60 min) psychological stress activates the HPA axis and the SNS and increases proinflammatory cytokine production. In contrast, in CFS patients, psychological stress induces similar or blunted activation of the HPA axis and the SNS and also suppresses proinflammatory cytokine production.

EFFECTS OF PSYCHOLOGICAL STRESS ON BODY TEMPERATURE

Some, but not all [41–43], CFS patients exhibit a low-grade fever or higher body temperature compared to healthy subjects [40, 44–46]. However, the mechanisms for why CFS patients display a low-grade fever are not fully understood and little attention has been paid to the role of psychological stress in the low-grade fever of CFS patients.

Animal studies have demonstrated that many kinds of psychological stress increase core body temperature (Tc) [47, 48]. Acute exposure to anxiety-provoking psychological stress induces a transient, monophasic increase in Tc [49]. Acute stress-induced hyperthermia is, at least in part, regulated by SNS-mediated non-shivering thermogenesis in brown adipose tissue (BAT), not by prostaglandin E_2, a principal fever mediator, or proinflammatory cytokines [47, 50]. Repeated application of psychological stressors slightly elevates Tc (around 0.2–0.3°C) in both light and dark periods [51, 52]. Such slightly higher Tc can be observed even several days after cessation of the final stress exposure [52]. Figure 2 shows the diurnal Tc changes in rats after exposure to repeated social defeat stress (1 hour daily for 28 days) on a stress-free day eight days after the final defeat. Repeatedly stressed animals

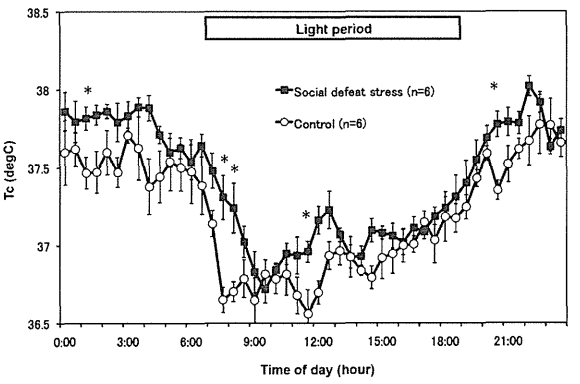

Fig. 2. Effects of repeated psychosocial stress on Tc in rats. Diurnal Tc changes in rats eight days after exposure to repeated (28) social defeat sessions (■, $n=6$) or control rats (○, $n=6$). Data represent mean ± SEM. *$p<0.05$ compared with control. (Adopted from (52) with permission).

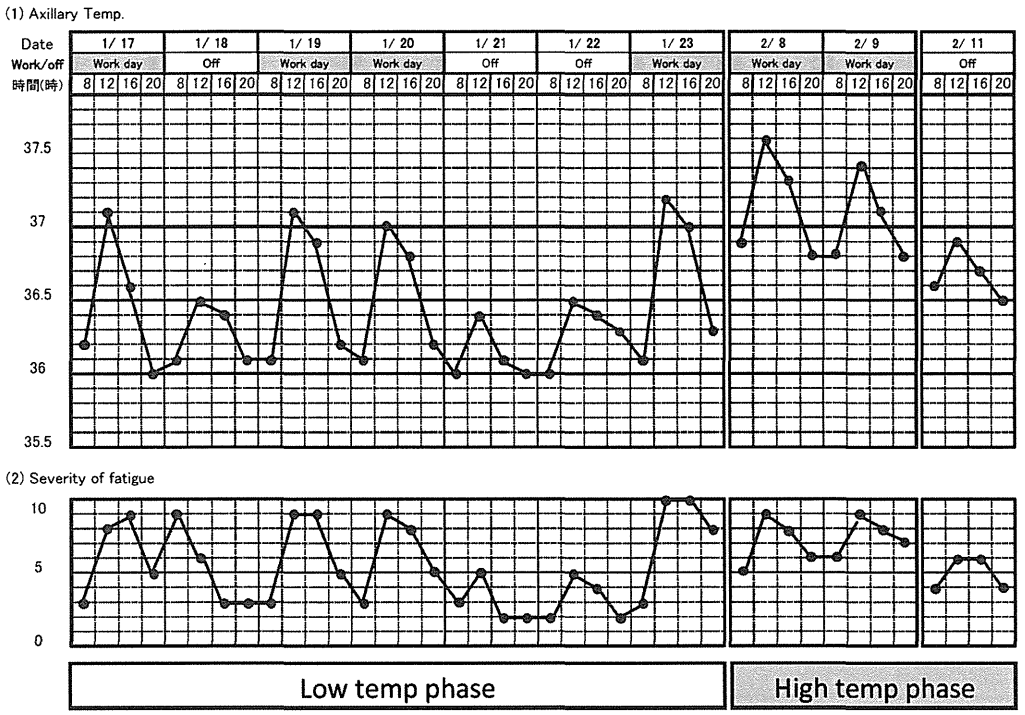

Fig. 3. Changes in axillary temperature and fatigue in a 24-year-old CFS patient. The temperature and severity of fatigue, as assessed by numerical rating scale with the severest fatigue as 10 and no fatigue as 0, was recorded at 8 a.m., 12 a.m., 4 p.m., and 8.p.m. (Adopted from [40] with permission).

also display an enhanced hyperthermic response to a novel stress [53, 54] via enhanced sympathetic nerve-mediated thermogenic actions [55, 56] and also exhibit depressive-like behavior [52].

Stress-induced hyperthermia is observed in human subjects as well. However, in healthy subjects, this phenomenon is less remarkable than that observed in small animals [57, 58]. In contrast, there are CFS patients who clearly show a higher Tc during stressful periods versus non-stressful ones. For example, some CFS patients show "workday hyperthermia", i.e., higher axillary temperatures on working days compared with holidays [46]. Figure 3 shows the record of axillary temperature and severity of fatigue of a 24-year-old woman with CFS. It demonstrates that her axillary temperature and fatigue scores were higher during working days compared to days off. The higher temperature may not be due to increased activity during the working day, but due to psychological strain since, as she was a telephone operator, she remained sitting almost all day but kept concentrating on numerous phone conversations.

Another example is the remarkable emotional stress-induced hyperthermic response in CFS patients. A 26-year-old female nurse with CFS noticed that she had an especially high axillary temperature (up to 38.5°C) when she felt stress at work. Therefore, to assess how psychological stress affects body temperature and to investigate the possible mechanisms for this hyperthermia, we conducted a 60-minute stress interview. In the interview, we asked her to recall and talk about her difficult life. Her axillary temperature at baseline was 37.2°C, and increased to 38.2°C (a 1.0°C increase) by the end of the interview. In contrast, her fingertip temperature decreased during the interview, indicating an inhibition of heat dissipation (Fig. 4) [40]. During the stress interview, her HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and plasma levels of noradrenaline and adrenaline increased. There were no significant changes in pyretic cytokines such as IL-1β and IL-6, or antipyretic cytokines such as TNF-α and IL-10. Rather serum levels of IL-6 and TNF-α slightly decreased during and after the stress interview (Table 2). Therefore, stress interview-induced remarkable hyperthermia may be mediated by negative emotion-associated SNS activation, not by pyretic cytokine production. Considering the findings on the effects of chronic stress on acute stress-induced hyperthermia in animals, it is possible that the CFS patient's difficult life acts as a chronic stressor, leading the

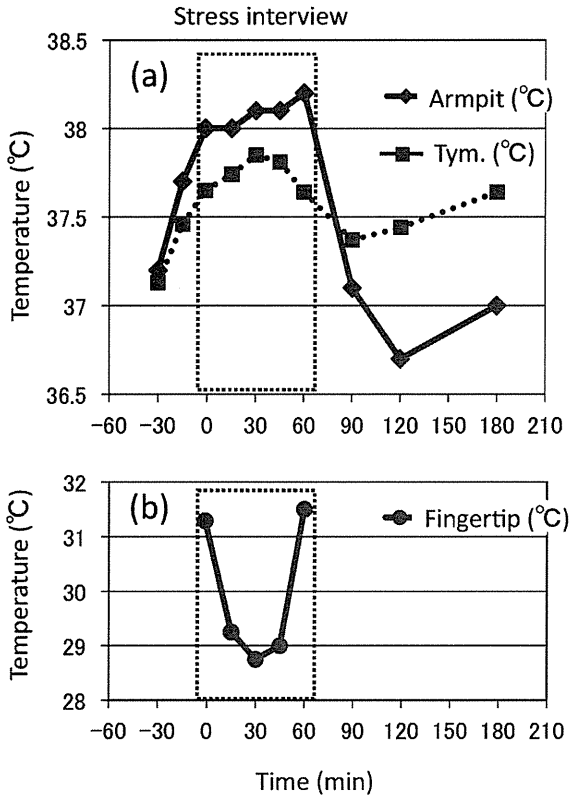

Fig. 4. Effects of stress interview on core and peripheral temperatures in a 26-year-old CFS patient. Changes in axillary (armpit) and tympanic membrane (tym.) temperatures (a) and fingertip temperature (b) during and after a 60-minute stress interview. Stress interview was conducted between 0 min and 60 min. (Adopted from (40) with permission).

patient to exhibit robust increases in Tc when she is exposed to emotional events.

DISCUSSION

This article demonstrated that psychological factors are involved in the onset, exacerbation, and/or relapse of CFS, and that early life stress acts as a risk factor to develop CFS in later life (Fig. 1).

Previous studies suggest that CFS patients exhibit HPA axis hypofunction, ANS dysfunction characterized by sympathetic overactivity and low vagal tone, and enhanced inflammation. Glucocorticoids inhibit the production and release of proinflammatory cytokines. SNS activation can be both pro- and anti-inflammatory depending on the type of adrenergic receptors activated [59]. Stimulation of the vagus nerve exerts anti-inflammatory actions by inhibiting proinflammatory cytokine release [60, 61]. Thus,

Table 2
Effects of stress interview on cardiovascular parameters, cytokines, and catecholamines. Stress interview was conducted between 0 min and 60 min. (Adopted from [40] with permission)

	9 am	Pre	30 min	60 min	120 min	180 min
IL-1β (pg/ml)	0.39	0.29	0.3	0.33	0.28	0.37
IL-6 (pg/ml)	2.9	3.1	1.8	1.9	3.6	3.3
TNF-a (pg/ml)	1.5	1.3	1.4	1.1	1	1.5
IL-10 (pg/ml)	<2	<2	<2	<2	<2	<2
A (pg/ml)		36	65	59	36	
NA (pg/ml)		298	409	431	285	
DA (pg/ml)		9	10	14	<5	
SBP (mmHg)	100	116	126	121	122	106
DBP (mmHg)	66	79	97	93	77	75
HR (mmHg)	72	92	103	102	83	86

A: adrenaline; DA: dopamine; DBP: diastolic blood pressure; HR: heart rate; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; min: minutes; NA: noradrenaline; SBP: systolic blood pressure; TNF-α: tumor necrosis factor-α.

stress systems of CFS patients are prone to facilitate increased proinflammatory cytokine production. As proinflammatory cytokines induce sickness behavior such as fatigue and pain [62], which is comparable to CFS symptoms, and psychological stress increases these cytokines [63, 64], it is reasonable to hypothesize that psychological stress may precipitate, perpetuate, or exacerbate CFS symptoms by proinflammatory cytokine production.

However, results from previous studies that investigated the effects of laboratory stress do not necessarily support this hypothesis because several contrasting findings were obtained, i.e., impaired sympathetic activation and decreased cytokine production in CFS patients (Table 3). It could be criticized that the duration of laboratory stress is too short or too weak to replicate the effect of life event stress or daily life stress to which CFS patients are exposed. However, considering that higher ratings of CFS symptom severity were associated with weaker SBP reactivity to psychological stress [39], sympathetic activation and proinflammatory cytokine production may not be the only explanation for the exacerbating effect of psychological stress on CFS. Further studies are necessary to address the biological mechanisms of how psychological stress exacerbates CFS.

This article demonstrated that psychological stress also contributes to low-grade fever in CFS patients. Although a subset of CFS patients exhibit low-grade fever, the role of psychological stress in this phenomenon has not been investigated. Animal studies have demonstrated that chronic stress induces hyperplasia of BAT, a heat-generating tissue [55], and increases uncoupling protein 1 (a heat-generating pro-

Table 3
Effects of laboratory psychological stress on neuroendocrine, autonomic, and immune functions in CFS patients and control subjects

Laboratory stress	Subjects	Parameters	Stress response vs. healthy subjects	Reference
Anagram task stress for 20 min	Adult CFS pt. (mean age, 37 y) vs. musclar dystrophy (MD) pt. and psychiatric pt. (P, anxiety and depressive disorders)	Physical and psychoilogical symptom scores by Symptom-emotion checklist	Increase in physical and psychological symptom scores in CFS and P groups but not in MS group	(34)
Mental arithmetic stress (−17) from four-digit number down to zero	Adult CFS pt. (mean age 33.6 y) vs. healthy subjects	Performance, BP, HR,	Same performance with less mistakes in CFS pts compared with controls. Increase in SBP, DBP, HR in both groups. Delta HR: lower in CFS pts vs. controls. Delta SBP and DBP: n.d.	(38)
Cognitive stress including stroop color/word interference test, symbol digit modalities test, trail making test, and mental arithmetic test (−13 from 100) for 16 min	Female CFS pt. (mean age, 34 y) vs. healthy subjects	BP, HR	Increase in SBP, DBP, and HR in both groups. Delta SBP, DBP, and HR: lower in CFS pts vs. controls. Pts with the lowest cardiovascular reactivity had the highest rating of CFS symptom severity	(39)
Trier social stress test for 14 min	Adult CFS pt. (mean age 36.0 y) vs. healthy subjects	HR, plasma ACTH and cortisol, salivary free cortisol	CFS pts had higher overall HR vs. controls. Increase in HR: n.d. Increase in plasma ACTH and plasma and salivary cortisol in both groups. ACTH response: weaker in CFS pts vs. controls. Plasma and salivary cortisol responses: n.d.	(35)
Trier social stress test for 14 min	Adult CFS pt. (mean age 36.0 y) vs. healthy subjects	(plasman ACTH and cortisol, salivary free cortisol) Number of leukocytes and monocytes. LPS-induced IL-6 and TNF-α	Increase in the number of leukocytes: n.d. The number of monocytes didn't change in both groups. In control, stress increased LPS-induced IL-6 and TNF-α. In contrast, stress decreased these cytokines in CFS pts	(36)
Mental arithmetic stress (−7) for around 80 sec	Adolescent CFS pt. (12–18 y) vs. healthy subjects (12–18 y)	BP, HR, acral skin blood flow (ASBF)	Increase in SBP, DBP, and HR: n.d. Decrease in ASBF: n.d.	(37)
Stess interview for 60 min	26 year old female CFS pt.	BP, HR, plasma CA, temperatures, serum II-1β, IL-6, TNF-α, IL-10	Increase in SBP, DBP, and HR. Increase in axillary and tympanic membrane temperature. Serum IL-6 and TNF-α were suppressed. IL-1β and IL-10 did not change	(40)

n.d., not significantly different between CFS patients and control subjects.

tein) expression and its function [56] in BAT. This is one reason why exposure to a novel stressor may induce remarkable hyperthermic responses in chronically stressed rats. Therefore, one possible explanation for psychological stress-induced exacerbation of low-grade fever in CFS patients is that chronic stress produces a vulnerability to hyperthermia when patients are exposed to acute emotional stress.

There is no doubt that psychological stressors influence CFS, and especially the severity of CFS. On the other hand, studies also suggest that the severity of CFS symptoms can be affected by how patients respond to psychological stress or social factors as well. CFS patients respond to and cope with psychological stress in either an adaptive or maladaptive way. It is suggested that emotional distress responses to stressors are a predictor of the likelihood and severity of CFS relapse and functional impairment [30]. Self-critical perfectionism is associated with the generation of daily hassles [65]. In contrast, optimism and social support buffer the illness burden [30].

CONCLUSIONS

Psychological factors are involved in CFS onset, exacerbation, and/or relapse, while early life stress acts as a risk factor for the development of CFS. CFS

patients respond to laboratory stress in a different way than healthy subjects, i.e., when compared with healthy subjects, CFS patients show a similar or blunted activation of the HPA axis and SNS and suppression of proinflammatory cytokines, whereas psychological stress increases these cytokines in healthy subjects. So far, it is not known how such differences contribute to the pathophysiology of CFS. Further studies are necessary to determine whether laboratory stress fully replicates typical daily stress and how these stress responses are related to psychological stress-induced exacerbation of CFS symptoms.

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