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論文内容の要旨

Second pain processing traced by electro- and magneto- encephalography in humans

It is known that there are two kinds of pain sensation, a sharp or pricking pain associated with rapidly conducting Aδ-fibers (first pain), and a dull or burning pain associated with slowly conducting C-fibers (second pain). We activated C-fibers selectively by stimulating a tiny area of the skin with a CO_2 laser beam using a thin aluminum plate with numerous tiny holes as a spatial filter. Using this new method, we successfully recorded C-fiber discharges with a microneurographic study and cortical responses evoked by C-fiber stimulation using electroencephalography (EEG) and magnetoencephalography (MEG) in humans.

First, we investigated C-fiber discharges and cerebral potentials evoked by weak CO_2 laser beams applied to a tiny skin area in five healthy subjects. Microneurography was recorded from the peroneal nerve in the right popliteal area. Cerebral potentials were recorded from the Cz electrode (vertex, based on the international 10-20 system) referred to linked earlobes. The mean conduction velocity (CV) of the five stable single units was 1.1±0.3 m/s. The mean latency of the positive peak of the cerebral potentials was 1327.4±46.2 ms, which was markedly longer than that from Aδ-fiber stimulation. In contrast, this stimulation method did not activate the Aδ units at all. These findings indicate that this new stimulation method selectively activates C-fiber nociceptors of the skin (Chapter 5 and Qiu et al., 2003).

Second, we measured the CV of C-fibers in the spinothalamic tract (STT) using this method. We delivered CO_2 laser pulses to tiny areas of the skin overlying the vertebral spinous processes at different levels from the 7^{th} cervical (C7) to the 12^{th} thoracic (T12), and recorded the cerebral evoked potentials in 11 healthy men. The mean CV of C-fibers in the STT was 2.2±0.6 m/s, which was significantly slower than that of the Aδ-fibers (10.0±4.5 m/s). This technique is novel and simple, and should be useful as a diagnostic tool for assessing the level of spinal cord lesions (Chapter 6 and Qiu et al., 2001).

Third, we evaluated the effects of attention, distraction and sleep on CO_2 laser-evoked potentials (LEP) related to C-fibers (ultra-late LEP), since the degree of perceived pain sensations is known to be influenced by the subjects' attention levels. CO_2 laser pulses were delivered to a tiny skin area of the dorsum of the right hand. Ultra-late LEP were recorded from 10 normal subjects in 5 different conditions: control (wakefulness), attention, distraction, drowsiness and sleep (stage 2). The amplitude of ultra-late LEP was slightly increased during attention and significantly decreased during distraction, relative to the control. The ultra-late LEP greatly decreased in amplitude or almost disappeared during sleep. We confirmed that the brain responses related to signals ascending through C-fibers were greatly affected by the level of consciousness, being consistent with the findings of late LEP related to Aδ-fibers. This is the first study indicating the important characteristics of ultra-late LEP related to consciousness, suggesting that they include cognitive function, and reporting that one has to be aware of changes in alertness when recording (Chapter 7 and Qiu et al., 2002).

Fourth, using MEG, we evaluated the cerebral regions related to second pain perception ascending through C-fibers and investigated the effect of distraction on each region. Thirteen normal subjects participated in this study. CO_2 laser pulses were delivered to the dorsum of the left hand to selectively activate C-fibers. The MEG responses were analyzed using a multi-dipole model. Results showed that (1) the primary somatosensory cortex (SI), and (2) the secondary somatosensory cortex (SII) - insula were the main generators for the primary component, 1M, the mean peak latency of which was 744 ms. In addition to (1) and (2), (3) the cingulate cortex and (4) the medial temporal area (MT) were also activated for the subsequent component, 2M, the mean peak latency of which was 947 ms. During a mental calculation task (distraction), all six sources were significantly reduced in amplitude, but the SII-insula ($P<0.01$) and cingulate cortex ($P<0.001$) were more sensitive than the SI ($P<0.05$) and MT ($P<0.05$). We confirmed that the SI in the contralateral hemisphere and the SII-insula, cingulate cortex and MT in the bilateral hemispheres play a major role in second pain perception, and all sites were greatly affected by changes in the attention levels, indicating that these regions are related to the cognitive aspect of second pain perception, and particularly to activities in the cingulate cortex (Chapter 8 and Qiu et al., 2004).

論文審査結果の要旨

痛覚には末梢のＡδ線維を介して伝えられる「速い痛み(first pain)」とより遅い伝導速度をもつＣ線維によって伝えられる「遅く、にぶい痛み(second pain)」があるとされている。しかし、これまでＣ線維のみを選択的に刺激する方法がなかったので、Ｃ線維の中枢投射機構の詳細は明らかでなかった。
申請者らは数多くの小さな穴をあけたアルミ板を通して比較的弱い CO_2 レーザーを皮膚に限局的に照射することによってＣ線維を選択的に刺激することを可能にし、これまで明らかにされてこなかったＣ線維から中枢への投射の経路と投射先を解析した。
まず申請者らは microneurography を用いて皮膚の電気刺激によって活性化される単一求心性神経線維軸索の活動電位を記録し、今回の新しい方法の適切さを検討した。すると今回電気刺激によって活性化され、記録された５本のＣ線維（伝導速度平均 1.1 ± 0.3m/s）はいずれも新しい CO_2 レーザー照射法によって活性化されたが、Ａδ線維は CO_2 レーザーの広範囲の刺激によって活性化されたが、今回の新しい手法では活性化されないことが確認された。

次に脳波でＣ線維刺激によって誘発される電位を頭蓋上 Cz の位置において記録し、脊椎にそって刺激するセグメントを系統的に変え、上行路の伝導速度を求めた。すると、CO_2 レーザー局所刺激法によって活性化されたＣ線維から入力を受ける脊髄上行路（脊髄視床路）の伝導速度は平均で 2.2 ± 0.6m/s と、やはり無髄線維であることが明らかになった。それに対して広範囲レーザー刺激によってＡδ線維を刺激した場合の上行路の伝導速度は 10.0 ± 4.5m/s で、それぞれ末梢と同様な伝導速度の上行路線維を経由することが明らかになった。

次に申請者らは脳磁場計測法を用いて、大脳皮質におけるＣ線維の投射先を調べた。その結果、反対側の SII 及び島、さらには帯状回皮質、と内側側頭葉及び同側の SII と島部に活性化が見られた。
そしてさらにこれらの皮質における末梢Ｃ線維由来の誘発脳磁場は刺激部位に注意を向けることで増強し、逆に暗算を行なうなどして注意をそらすと消失するというように注意や意識レベルによる修飾を受けることが明らかになった。

これらの知見はいずれもＣ線維を経由する second pain の中枢投射機構に関する新しい知見で、その科学的意義は大変高い。結果は既に国際誌に 4 編の論文として発表されており、高い評価を受けている。これらのことから申請者の論文は学位論文として十分にふさわしい内容であると審査委員会の委員全員一致で判定した。