Cerebral perfusion changes during cataplexy in narcolepsy patients

Abstract—To localize cerebral perfusion differences during cataplexy, brain SPECT subtraction was performed between cataplexy and baseline awake period or REM sleep in patients with narcolepsy. During cataplexy, subtracted SPECT showed hyperperfusion in right amygdala, bilateral cingulate gyri, basal ganglia, thalami, premotor cortices, sensorimotor cortices, right insula, and brainstem, and hypoperfusion in prefrontal cortex and occipital lobe. This result suggests that cataplexy is produced by the activation of amygdalo-cortico-basal ganglia–brainstem circuit.

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Cataplexy is a sudden loss of muscle tone triggered by emotional changes such as laughing and is caused by the inappropriate activation of descending neural pathways that promote atonia.[1] Although these same REM sleep atonia pathways likely help mediate cataplexy, the mechanisms differ slightly. In contrast to neurons of the locus ceruleus that are silent during both REM sleep and cataplexy, neurons of the dorsal raphe are silent during REM sleep but retain some activity during cataplexy in narcoleptic dogs.[2] The radiotracer for SPECT, ^{99m}Tc-ethylcysteinate dimer (ECD) has a high first-pass brain extraction rate, with maximum uptake being achieved within 30 to 60 seconds of an IV injection.[3] They become trapped in the brain, thereby producing a "snapshot" of the ictal cerebral perfusion pattern that can be imaged up to 4 hours after radiotracer injection in patients with epilepsy.

To investigate cerebral perfusion changes during cataplexy, we injected ^{99m}Tc-ECD during a cataplectic episode, REM sleep, and a baseline awake period for a brain SPECT study in two patients with narcolepsy.

Methods. Subject 1 was a 64-year-old man with a 35-year history of excessive daytime sleepiness (EDS) and daily episodes of cataplexy with head drooping and falling down. These episodes were triggered when he was sad or elated and lasted more than 3 minutes.

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Subject 2 was a 25-year-old woman. Her EDS and cataplexy began at age 15 years. Her cataplectic episodes started with a sagging of the face and head drooping and lasted for up to 5 minutes. Frequently, she would slump onto the ground. Her cataplectic attacks were triggered by talking to friends on the phone. She had vivid dreams and hypnagogic visual hallucinations. Both patients had overnight polysomnography and the Multiple Sleep Latency Test.

^{99m}Tc-ECD brain SPECT and cataplexy induction. Brain SPECT images were obtained 30 to 60 minutes after injecting of 25 mCi ^{99m}Tc-ECD using a three-headed Triad XLT system (Trionix Research Laboratory, Twinsburg, OH) equipped with low-energy, high-resolution collimators. The transaxial system resolution of this camera was 6.9 mm full width at half maximum. Images were reconstructed by filtered back-projection using a Butterworth filter. Attenuation correction was performed using Chang's method (attenuation coefficient $\mu = 0.12\ cm^{-1}$). The voxel dimension of reconstructed SPECT was $3.56 \times 3.56 \times 3.56$ mm (x, y, z, respectively).

^{99m}Tc-ECD for brain SPECT was injected during the baseline awake period, a cataplectic episode, and REM sleep in Subject 1 and during the baseline awake period and a cataplectic attack in Subject 2. During the SPECT studies, patients were continuously monitored using EEG, electro-oculography, and EMG.

SPECT subtraction. SPECT subtraction was performed on an offline workstation using ANALYZE 7.5 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). All biomedical images were transferred from scanner consoles to a Unix workstation using a digital audiotape device. The SPECT subtraction procedures were described in a previous study.[4,5]

Results. The results of sleep studies are summarized in table 1. Both patients had a very short sleep latency and five sleep-onset REM periods. Subject 1 had mild obstructive apnea-hypopnea syndrome. He had worn a nasal continuous positive airway pressure mask for more than 6 months, but his EDS did not decrease. Subject 2 showed only frequent arousals with no other problems during overnight polysomnography.

Subject 1 experienced a cataplectic episode using a sad story. Subject 2 was able to induce cataplexy by talking and laughing with a friend on the phone. During these episodes, both subjects presented with complete muscle atonia of the limbs, head, and trunk extensor muscles and loss of speech. Tendon reflexes were absent. EEG recordings showed alpha rhythm persistence on posterior head regions and submental EMG-documented hypotonia. They recovered from their cataplexies 5 minutes (Subject 1) and 3 minutes (Subject 2) after onset.

Subtracted SPECT. Hyperperfusion during cataplexy vs the awake period was observed in bilateral cingulate gyri and sensorimotor cortices, basal ganglia, right amygdale, and hippocampal head, thalami, midbrain, and midline pons (table 2; figure, A), whereas hypoperfusion was

Table 1 *The results of overnight polysomnography and Multiple Sleep Latency Test*

	Subject 1	Subject 2
Overnight polysomnography		
Sleep latency, min	2.5	5
REM sleep latency, min	85.5	2.5
Apnea-hypopnea index, per hour	6.4	0.6
Arousal index, per hour	20.4	15.3
Multiple Sleep Latency Test		
Mean sleep latency, min	0.4	1.5
Mean REM sleep latency, min	1	0.3
No. of SOREMPs	5	5

SOREMPs = sleep-onset REM periods.

Table 2 *Brain regions with perfusion changes during a cataplectic episode compared to awake state or REM sleep*

Hyperperfusion during cataplexy compared to awake period
- Subject 1
  - Bilateral frontal lobes: cingulate gyri, medial frontal, premotor cortices
  - Bilateral basal ganglia, bilateral thalami (L>R)
  - Right amygdala and hippocampal head
  - Bilateral sensorimotor cortices
  - Right insula cortex
  - Midline pons and bilateral midbrains
- Subject 2
  - Bilateral frontal lobes: cingulate gyri, premotor cortices
  - Bilateral basal ganglia, right thalamus
  - Right amygdala
  - Right sensorimotor cortex
  - Right insula cortex
  - Pons, right midbrain

Hypoperfusion during cataplexy compared to awake period
- Subject 1
  - Bilateral prefrontal cortices
  - Bilateral occipital cortices
- Subject 2
  - Bilateral prefrontal cortices
  - Bilateral occipital cortices

Hyperperfusion during cataplexy compared to REM sleep
- Subject 1
  - Bilateral sensorimotor cortices
  - Bilateral basal ganglia
  - Right amygdala and hippocampus
  - Bilateral cingulate gyri
  - Thalamus
  - Midbrain and pons

Hyperperfusion during REM sleep compared to cataplexy
- Subject 1
  - Bilateral occipital lobes
  - Left mid-posterior basal temporal cortex
  - Left mid-inferior parietal cortex
  - Right inferior parietal and posterior temporal cortices

detected in the bilateral prefrontal cortices and occipital lobes (figure, C).

Hyperperfusion during cataplexy vs REM sleep was observed in bilateral cingulate gyri, sensorimotor cortices, basal ganglia, thalami, right amygdala/hippocampus, midbrain, and pons (figure, B), whereas hyperperfusion during REM sleep compared to during cataplexy was detected in bilateral prefrontal cortices, right inferior parietal cortex, left mid-posterior parietal cortex, left mid-posterior basal temporal regions, and bilateral occipital lobes (figure, C).

Discussion. Neurons of the amygdala are frequently active when individuals show strong emotions, and stimulation of the amygdala can increase REM sleep, perhaps via its projections to the laterodorsal, pedunculopontine tegmental nuclei, and nearby regions.[6] In recordings from narcoleptic dogs, amygdala neurons often fire just before and during a cataplectic episode,[7] suggesting that they may help trigger the response. These observations support hyperperfusion of the right amygdala in our patients. Human REM sleep shows the predominant right hemisphere activation by SPECT imaging[8] and spectral EEG analysis.[9] Right amygdala activation in our patients suggests that the right hemisphere is also more activated during cataplexy. An fMRI study showed that the right amygdala was more activated by laughing or crying stimuli.[10]

The cingulate gyrus is related to emotional processes. An fMRI study showed that emotional pictures result in increased blood flow in the anterior cingulate gyri, dorsolateral frontal lobes, and amygdala/anterior temporal regions.[11] Our results suggest that the overactivation of the amygdala and cingulate gyrus in response to emotional changes may trigger a cataplectic pathway.

A previous SPECT study showed significant hypoperfusion in bilateral premotor cortices, cingulate gyri, and sensorimotor cortices in the baseline state of patients with narcolepsy with cataplexy,[12]; however, we found hyperperfusion during a cataplectic episode. These observations suggest that cataplexy may be related to increased neuronal discharges in specific brain regions involved in the baseline state of patients with narcolepsy.

Our study demonstrated basal ganglia hyperperfusion during a cataplectic episode. Postsynaptic D2-receptor binding was elevated in narcolepsy and correlated with the frequency of cataplectic attacks.[13] In narcoleptic dogs, local perfusion with D2-receptor agonists into the globus pallidus/putamen produced an increase in cataplexy in narcoleptic canines,[14] whereas oral administration of dopamine D2/D3 antagonist in canine narcolepsy significantly reduced cataplexy.[15]

We also found hyperperfusion in the midbrain and pons during a cataplectic episode. Canine experiments have identified several monoamine receptor subtypes that are involved in the regulation of cataplexy, namely, adrenergic postsynaptic a-1b,[16] presynaptic a-2,[17] and dopaminergic D2/D3 receptors.[18] Furthermore, the acting sites of D2/D3 compounds have also been identified recently; D2/D3 agonists perfused into the ventral tegmental area, substantia nigra, and diencephalic dopamine cell groups, such as A11, significantly aggravate cataplexy, whereas

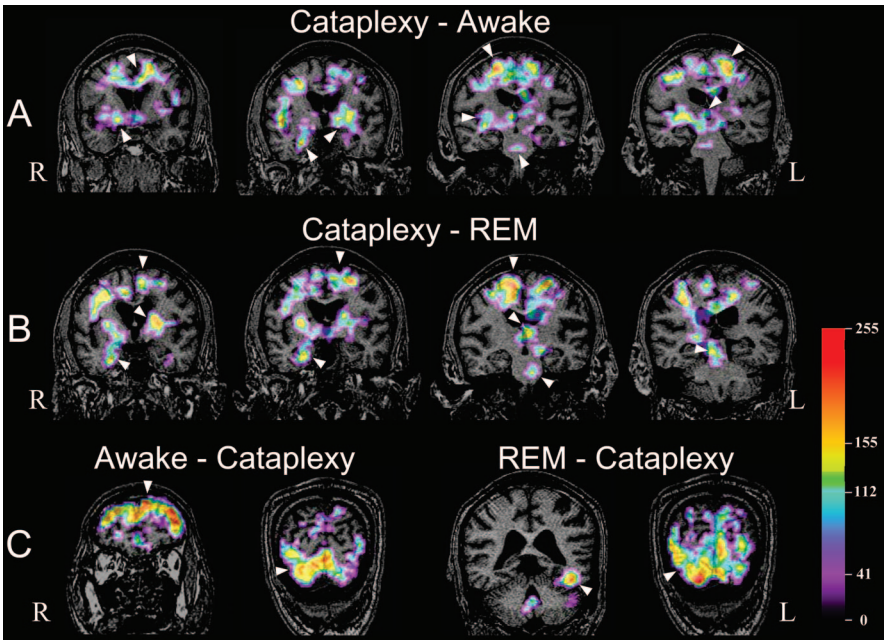

Figure. SPECT subtraction results. (A) Hyperperfusion in bilateral premotor cortices, cingulate gyri, sensorimotor cortices, basal ganglia, right amygdala/hippocampus, right insula, both thalami, and brainstem during cataplectic episode compared to baseline awake period (brain SPECT during cataplexy − brain SPECT during baseline awake period). (B) Hyperperfusion in sensorimotor cortices, cingulate gyri, basal ganglia, thalami, right amygdala/hippocampus, midbrain, and pons during cataplexy compared to REM sleep (brain SPECT during cataplexy − brain SPECT during REM sleep). (C, left two images) Hyperperfusion in prefrontal cortices and occipital lobes during awake period compared to cataplexy (brain SPECT during awake period − brain SPECT during cataplexy). (C, right two images) Hyperperfusion in left posterior basal temporal cortex and bilateral occipital lobes during REM sleep compared to cataplexy attack (brain SEPCT during REM sleep − brain SPECT during cataplexy). Small arrowheads indicate brain structures described.

D2/D3 antagonists significantly reduce cataplexy.[19,20] These data suggest that cataplexy is produced by an episodically overactive neuronal state of basal ganglia and specific brainstem nuclei.

Although it is difficult to differentiate structures related to a strong emotion from those accompanying a cataplectic attack, sudden emotional changes may activate the right amygdala and cingulate gyri. Then these structures trigger the activation of a cataplectic pathway consisting of sensorimotor cortex, basal ganglia, and brainstem nuclei.

Cataplexy was suggested as an atavistic expression of tonic immobility (TI) rather than REM sleep atonia.[21] TI describes a response pattern characterized by severe motor inhibition when an animal faces grave danger. Both TI and cataplexy make use of the brainstem regions responsible for REM sleep atonia as a final common pathway to induce the spinal inhibition of motor neurons,[22,23] but cerebral perfusion changes during TI have not been studied.

References 11 through 23 may be found on the *Neurology* Web site at www.neurology.org.

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