Acetazolamide Reactivity in Atherothrombotic, Cardioembolic and Lacunar Infarctions

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Abstract. Ten cases of atherothrombotic brain infarction, 10 cases of cardioembolic brain infarction, 10 cases of lacunar brain infarction, 10 cases of transient ischemic attack (TIA) and 10 age-matched controls were studied. The cerebral blood flows in the cerebral cortex and cerebral white matter were significantly lower in the atherothrombotic, cardioembolic and lacunar infarction groups than in the TIA and control groups. The acetazolamide reactivity in the cerebral cortex was significantly lower in the atherothrombotic and lacunar infarction groups than in the cardioembolic, TIA and control groups. The rate of association of hypertension was significantly higher in the atherothrombotic, lacunar and TIA groups than in the cardioembolic and control groups. Plasma fibrinopeptide A, platelet factor 4 and β-thromboglobulin concentrations were higher in the atherothrombotic, cardioembolic and lacunar groups than in the TIA and control groups. The present study suggests that the degree of thrombolysis and platelet activation is less in TIA than in cerebral infarction and that underlying cerebral arteriosclerosis is more severe in atherothrombotic and lacunar infarction than in cardioembolic infarction.

Key words: cerebral infarction, transient ischemic attack, xenon computed tomography

Introduction

According to the Special Report from the National Institute of Neurological Disorders and Stroke, brain infarction is commonly considered to be atherothrombotic, cardioembolic, or lacunar. Atherothrombotic infarction includes artery-to-artery embolism. Subcortical cystic infarcts with a diameter less than 1.5 cm are classified as lacunar infarction. Focal brain dysfunction is divided into transient ischemic attacks (TIAs) and stroke. Episodes of focal brain dysfunction lasting less than 24 hours are classified as TIAs.

In order to find out the differences in regional cerebral blood flows and cerebrovascular acetazolamide reactivity among atherothrombotic, cardioembolic and lacunar infarctions and TIAs, xenon computed tomography (CT) cerebral blood flow studies were performed before and after injection of acetazolamide in the acute stage.

Patients and Methods

Ten cases of atherothrombotic brain infarction, 10 cases of cardioembolic brain infarction, 10 cases of lacunar brain infarction, 10 cases of TIA and 10 age-matched controls were studied with their informed consent. The subjects were selected according to the date of admission. We excluded the patients whose diagnosis is not certain. The xenon CT study was performed within two weeks from the onset.

The regional cerebral blood flows were measured using the stable xenon CT method. The subjects inhaled room air followed by a mixture of 30% xenon and 50% oxygen for 3 minutes. Serial scanning was performed once before xenon inhalation, three times in the wash-in process and five times in the washout process of 5 minutes. The xenon concentration in the end-tidal expired gas was continuously recorded by the thermoconductivity method. We used the xenon delivery and analysis system (AZ-7000 model, Anzai Sogyo, Tokyo, Japan) and the CT equipment (PreSage, Yokogawa Medical Systems, Tokyo, Japan). Round regions of interest (ROIs) with a diameter of 7 mm were placed in the cerebral cortex and cerebral white matter where the influence of cerebral infarction was considered to be little. The regional cerebral blood flows were measured before and 20 minutes after intravenous injection of 17 mg/kg acetazolamide and the cerebrovascular acetazolamide reactivity (increase rate of regional cerebral blood flows by acetazolamide) was calculated.

Results

Figure 1 shows the xenon CT cerebral blood flow studies. Before injection of acetazolamide,
cerebral blood flows were decreased not only in the infarct area but also in the contralateral hemisphere in atherothrombotic, cardioembolic and lacunar infarctions. The increase rate of cerebral blood flow by injection of acetazolamide was low in atherothrombotic infarction and slightly low in lacunar infarction.

Table 1 shows the statistical analysis. The cerebral blood flows in the cerebral cortex and cerebral white matter were significantly lower in the atherothrombotic, cardioembolic and lacunar infarction groups than in the TIA and control groups. The acetazolamide reactivity in the cerebral cortex was significantly lower in the atherothrombotic and lacunar infarction groups than in the cardioembolic, TIA and control groups. The rate of association of hypertension was significantly higher in the atherothrombotic, lacunar and TIA groups than in the cardioembolic and control groups. Plasma fibrinopeptide A, platelet factor 4 and β-thromboglobulin concentrations were higher in the atherothrombotic, cardioembolic and lacunar groups than in the TIA and control groups.

Discussion

In the present study, blood flows in the cerebral cortex contralateral to the infarction were lower in the atherothrombotic, cardioembolic and lacunar infarction groups than in the control group. Large cerebral infarction may decrease the blood flow in the contralateral cortex but lacunar infarction is too small to decrease the blood flow in the contralateral cortex. Therefore, widespread cerebral arteriosclerosis is considered to be present as the basis of lacunar infarction.

Acetazolamide dilates cerebral arterioles by inhibiting carbonic anhydrase and increasing arteriolar CO₂, and is useful for examining cerebrovascular dilatory reserve capacity. The result that cerebrovascular acetazolamide reactivity in the cerebral cortex contralateral to the infarction was lower in the atherothrombotic and lacunar infarction groups than in the cardioembolic infarction group in the present study suggests that cerebrovascular dilatory reserve capacity is less in atherothrombotic and lacunar infarction than in cardioembolic infarction.

Fibrinopeptide A⁹,¹⁰ is a marker of thrombolysis and platelet factor 4 and β-thromboglobulin¹¹,¹² are markers of platelet activation. The result that plasma fibrinopeptide A, platelet factor 4 and β-thromboglobulin concentrations were higher in the atherothrombotic, cardioembolic and lacunar infarction groups than in the TIA group in the present study suggests that the degree of thrombolysis and platelet activation is less in TIA than in cerebral infarction.

The results that the cerebrovascular acetazolamide reactivity in the cerebral cortex contralateral to the infarction was lower and the rate of association of hypertension was higher in atherothrombotic, cardioembolic and lacunar infarction groups than in the TIA group in the present study suggests that the degree of thrombolysis and platelet activation is less in TIA than in cerebral infarction.
Table 1: Underlying Conditions, Cerebral Blood Flow and Acetazolamide Reactivity

<table>
<thead>
<tr>
<th></th>
<th>atherothrombotic</th>
<th>cardioembolic</th>
<th>lacunar</th>
<th>TIA</th>
<th>control</th>
</tr>
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<tbody>
<tr>
<td>Number of cases</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<tr>
<td>Age</td>
<td>64±9</td>
<td>62±8</td>
<td>65±5</td>
<td>61±7</td>
<td>63±8</td>
</tr>
<tr>
<td>Male:female</td>
<td>6:4</td>
<td>7:3</td>
<td>6:4</td>
<td>5:5</td>
<td>6:4</td>
</tr>
<tr>
<td>Carotid plaque</td>
<td>10×</td>
<td>0</td>
<td>0</td>
<td>10×</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7×</td>
<td>2</td>
<td>6×</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>History of TIA</td>
<td>3×</td>
<td>0</td>
<td>0</td>
<td>4×</td>
<td>0</td>
</tr>
<tr>
<td>Fibrinopeptide A (ng/ml)</td>
<td>11.2±3.1×</td>
<td>9.4±2.2×</td>
<td>10.2±2.9×</td>
<td>7.1±2.3</td>
<td>6.8±2.1</td>
</tr>
<tr>
<td>Platelet factor 4 (ng/ml)</td>
<td>27.3±6.9×</td>
<td>19.2±6.2×</td>
<td>24.8±6.4×</td>
<td>13.7±5.5</td>
<td>13.2±5.7</td>
</tr>
<tr>
<td>β-Thromboglobulin (ng/ml)</td>
<td>81.8±18.5×</td>
<td>57.3±15.2×</td>
<td>73.6±17.8×</td>
<td>41.4±13.6</td>
<td>39.2±14.2</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/100g/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cerebral cortex</td>
<td>32.8±5.6×</td>
<td>40.6±5.8×</td>
<td>41.4±5.9×</td>
<td>50.1±6.6</td>
<td>52.3±6.8</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>19.4±3.2×</td>
<td>21.3±3.6×</td>
<td>22.0±3.7×</td>
<td>24.8±4.1</td>
<td>25.9±4.3</td>
</tr>
<tr>
<td>Acetazolamide reactivity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>39.1±6.8×</td>
<td>53.6±7.8×</td>
<td>41.5±6.9×</td>
<td>53.4±8.1</td>
<td>54.3±8.2</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>27.4±4.9×</td>
<td>32.7±5.2×</td>
<td>31.8±5.1</td>
<td>36.6±6.2</td>
<td>37.5±6.3</td>
</tr>
</tbody>
</table>

*a* P<0.01 compared with the cardioembolic, lacunar and control groups.
* b P<0.01 compared with the other 4 groups.
* c P<0.01 compared with the cardioembolic and control groups.
* d P<0.01 compared with the TIA and control groups.
* e P<0.01 compared with the cardioembolic, TIA and control groups.

the atherothrombotic and lacunar infarction groups than in the cardioembolic infarction group suggest that underlying cerebral arteriosclerosis is more severe in atherothrombotic and lacunar infarction than in cardioembolic infarction.13,14

References

The Value of Acetazolamide Challenge Test in the Evaluation of Acute Stroke

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Abstract. The acetazolamide (ACZ) challenge test provides a useful information about compromised hemodynamic state in chronic stroke. However, there is no consensus whether this test is of any value in the evaluation of acute ischemic stroke. The purpose of this study is to examine the value of ACZ challenge test in the management of acute ischemic stroke.

Study 1: Nineteen patients with acute embolic stroke were subjected to the Xe CT with and without ACZ (17 mg/kg, i.v.) within 6 hours from the onset. The cases included 12 middle cerebral artery (MCA) occlusions and 7 internal carotid artery (ICA) occlusions. The baseline cerebral blood flow (CBF) values and cerebrovascular reserve (CVR) (% increase in CBF after ACZ) were analyzed in 53 affected regions of interest (ROI). The study indicated that the CBF threshold of subsequent permanent infarction was 15 ml/100g/min and the ROI with negative CVR had a higher incidence of hemorrhagic infarction. Study 2: Xe-CT with and without ACZ was performed in 32 patients with acute occlusion of the main trunks of cerebral arteries within 6 hours after the onset. Occluded arteries were MCA in 20 patients, ICA in 7, both ICA and MCA in 4 and anterior cerebral artery (ACA) in one. The abnormal hemispheric CBF (<20 ml/100g/min) and CVR (<10%) were correlated with the Glasgow outcome scales of the patients. The predictability of Good Recovery, Moderately Disabled, Severely Disabled, Vegetative Survival and Dead were 80%, 50%, 50%, 100% and 100% by CBF criteria, and 80%, 60%, 80%, 100% and 100% by CVR criteria, respectively. There was no significant increase in the predictability of final outcome of the patients by adding the CVR information of the acute stage. The ACZ challenge test has a potential value in the prediction of hemorrhagic transformation of the ischemic regions. It does not increase the predictability of the long-term outcome. We do not recommend performing ACZ challenge test on routine basis in the evaluation of acute ischemic stroke.

Key words: Xenon CT, stroke, acetazolamide, outcomes

Introduction

It is widely accepted that the acetazolamide (ACZ) challenge test provides a useful information about compromised hemodynamic state. However, whether this test is useful or not in the evaluation of acute cerebral ischemia is still controversial. The purpose of our study is to examine the value of ACZ challenge test in the management of acute stroke. We have examined if the ACZ challenge test can be a good predictor of immediate or long-term outcome. In the first study, we examined the occurrence of hemorrhagic and ischemic infarction in the ischemic areas. In the second study, we correlated the initial hemodynamic parameters to clinical outcomes.

Material and Methods

1. Early outcomes

Nineteen patients with acute embolic stroke were subjected to the Xe CT with and without ACZ injection within 6 hours from the onset according the method described previously. The cases included 12 middle cerebral artery (MCA) occlusions and 7 internal carotid artery (ICA) occlusions. Ten of them were treated conservatively, and 9 treated with intraarterial injection of urokinase. There were 28 regions of interest (ROI) examined in the conservatively treated group and 25 in the thrombolytic group. The total number of ROI examined were 53.

2. Late outcomes

Thirty-two patients were included in this study. Xe-CT was carried out within 6 hours from the onset. Occluded arteries were MCA in 20 patients, ICA in 7, both ICA and MCA in 4 and the anterior cerebral artery (ACA) in one. The outcomes were assessed using GOS at 3 months from the onset.
Results

1. Early outcomes

CBF thresholds of permanent infarction was 15, and 20 ml/100 g/min in groups with conservative treatment and intraarterial thrombolysis, respectively. In the conservatively treated group, CBF values of ROI with hemorrhagic transformation ranged from 5 to 33 ml, but all of them showed the ACZ responses less than 0 ml. When all ROIs were analyzed, the incidence of hemorrhagic transformation was 10 out of 21 in the ROIs with CVR less than 0, and 4 out of 32 in the ROIs with CVR equal or greater than 0 ml/100 g/min. This difference was statistically significant with a chi-square test.

2. Late outcomes

The abnormal hemispheric CBF (<20 ml/100g/min) and CVR (<10%) were correlated with the Glasgow outcome scales 3 months after the onset. The predictability of Good Recovery, Moderately Disabled, Severely Disabled, Vegetative Survival and Dead were 80%, 50%, 50%, 100% and 100% by CBF criteria, and 80%, 60%, 80%, 100% and 100% by CVR criteria, respectively. There was no significant increase in the predictability of final outcome of the patients by adding the CVR information of the acute stage.

Discussion

The results indicated that a baseline CBF value is not a good predictor of the hemorrhagic transformation of the ischemic areas, but abnormal ACZ response was highly suggestive of high rate of hemorrhagic transformation. In this sense, the ACZ test can have some value in the initial evaluation of acute stroke. ACZ challenge test may delineate the degree of tissue damage and subsequent hemorrhagic transformation more efficiently. And this information is useful to select the patients for acute interventions. However, it takes at least extra 20 min and can be associated with local and systemic side effects such as intracranial steal or systemic acidosis. We cannot neglect these disadvantages especially in the unstable patients.

Conclusions

The ACZ challenge test has a potential value for predicting hemorrhagic transformation of the ischemic areas in acute embolic stroke. But it is not useful to predict late clinical outcomes. When we consider its practical and theoretical disadvantages, we do not recommend a routine use of ACZ challenge test in the evaluation of acute stroke.

References

Activation of Fronto-Limbic System in the Human Brain by Cigarette Smoking: Evaluated by a CBF Measurement

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Abstract. Nicotine produces profound behavioral effects in humans, but little is known about the sites of its action. There is a hypothesis that frontal lobe and limbic/cingulate cortical structures might be the sites. In this study, we examined the effects of cigarette smoking on feeling and cerebral blood flow (CBF) in human subjects.

Young and healthy 9 cigarette smokers (all males, 24-33 years, average, 26.4) were included. After prohibiting them from smoking for 15 hours, CBF was measured using a Xenon CT-CBF system. Fifteen minutes later after allowing them to smoke two pieces of cigarette, the second CBF measurement was performed. Subtraction CBF map was created to display the changes after smoking. CT images were taken at three levels so as to include the cerebral lobes, basal ganglia, limbic system, brainstem and cerebellum.

Arterial nicotine increased up to the levels 8 times higher than before smoking. The increases of blood pressure and pulse rate were minimal. Arterial carbon dioxide level and hematocrit did not change. Feeling after smoking was variable in individual subject. In 8 subjects with a relatively high feeling, CBF increased mainly in the frontal lobe, hippocampus, uncus, thalamus and caudate nucleus. CBF did not change in the parietal, temporal and occipital lobes, and in the putamen, insula, brainstem and cerebellum. In two subjects with uncomfortable feeling, CBF did reduce in the whole brain.

The CBF increase in frontal lobe and limbic structures seems to be secondary to nicotine-induced neuronal activation in each structure. Mesocorticolimbic dopamine system, which is believed to influence learning, memory or emotional performance, appears to be a target for nicotine. The CBF reduction in the whole brain might be due to cerebral vasoconstriction or be secondary to a systemic hypotension.

Key words: cigarette smoking, feeling, cerebral blood flow, Xenon CT

Introduction

It is well known that cigarette smoking causes a constriction of many blood vessels with an increase in systemic arterial blood pressure and heart rate (Emoto et al., 1995; Seto et al., 1989). On the other hand, cerebral blood flow (CBF) is augmented, remains unaffected, or is reduced by cigarette smoking in normal subjects and asymptomatic individuals (Kuhn, 1967; Mitkov et al., 1971; Gotoh et al., 1972; Miyazaki, 1973, Skinhoj et al., 1973; Wennmalm, 1982; Dorrance et al., 1972; Kimura et al., 1989; Kodaira et al., 1993). No the sites of its action has been carried out concerning the effects of cigarette smoking on cerebral blood flow (CBF) using a Xenon computed tomography (Xenon CT-CBF) system in this study, we examined the effects of cigarette smoking on feeling and regional CBF in human subjects using a Xenon CT-CBF system.
was performed at 1, 2, 3, and 4 min. after the initiation of xenon inhalation in the washin phase and at 1, 2, 3, and 4 min. after the termination of xenon inhalation in the washout phase (4 minutes washin/4 minutes washout method). CT images were taken at three levels so as to include the cerebral lobes, basal ganglia, limbic system, brainstem and cerebellum. During the measurement of CBF, the subjects were requested to keep their eyes closed.

Systemic blood pressure and pulse rate were measured from the forearm in cigarette smoking before and after. For the measurement of PaCO₂, hematocrit, serum nicotine concentrations, arterial blood sampling was carried out at the beginning and end of the Xenon CT-CBF studies.

Regional CBF results were analyzed by region of interest (ROI) and subtraction CBF map to display the changes after smoking. Region of interests (ROIs) were outlined for 33 sites: frontal lobe, temporal lobe, occipital lobe, thalamus, cingulate gyrus, caudate nucleus, putamen, insula cortex, parahippocampal gyrus, rolandic area, uncus, brain stem and cerebellum.

Results

Both systolic and diastolic blood pressure were elevated a little in cigarettes smoking before and after. The increases pulse rate were also minimal. Arterial carbon dioxide level and hematocrit did not change. But, the serum nicotine concentrations increased up to the levels 8 times higher than before smoking (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before smoking</th>
<th>After smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sys BP (mmHg)</td>
<td>112±12</td>
<td>114±9.0</td>
</tr>
<tr>
<td>Dias BP (mmHg)</td>
<td>71±10</td>
<td>73±11</td>
</tr>
<tr>
<td>Pulse rate (min⁻¹)</td>
<td>67±10</td>
<td>79±13</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>45.4±3.9</td>
<td>44.7±1.2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>45±1.8</td>
<td>45.5±1.3</td>
</tr>
<tr>
<td>S. N.C. (ng/ml)</td>
<td>5.6±5.5</td>
<td>48.3±21.4</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.
Sys BP, systolic blood pressure. Dias BP, diastolic blood pressure. S.C.N., serum nicotine concentration.

The percentage increases in the regional cerebral blood flow after cigarettes smoking relative to those before are shown in a Table 2. Two of 10 subjects showed no change or slight reduction in whole cerebral blood flow.

In 8 subjects with high feeling, it is evident that the regional cerebral blood flow was increased after cigarettes smoking in the frontal lobe, occipital lobe, cingulate gyrus, caudate nucleus, putamen, para hippocampal gyrus, uncus, insular cortex and thalamus. Cigarettes smoking caused a significant increase of cerebral blood flow in the frontal lobe, para hippocampal gyrus and uncus (p<0.01).

Table 2 Mean regional cerebral blood flow (CBF) of cigarettes smoking before and after, determined in circular regions of interest with relatively high feeling. (ml/min/100g, n=8)

<table>
<thead>
<tr>
<th>Circumference regions of interest</th>
<th>Before smoking</th>
<th>After smoking</th>
<th>Percentage increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>45.4±5.6</td>
<td>48.4±6.7*</td>
<td>6.6</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>47.7±6.9</td>
<td>49.5±5.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>49.1±5.5</td>
<td>49.8±6.2</td>
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</tr>
<tr>
<td>Occipital lobe</td>
<td>35.5±6.3</td>
<td>37.7±6.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>61.4±11.1</td>
<td>61.3±15.0</td>
<td>-0.2</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>50.2±8.6</td>
<td>58.3±14.4**</td>
<td>16.1</td>
</tr>
<tr>
<td>Putamen</td>
<td>48.0±10.7</td>
<td>53.6±14.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Para hippocampal gyrus</td>
<td>42.2±5.6</td>
<td>48.0±5.9*</td>
<td>13.7</td>
</tr>
<tr>
<td>Uncus</td>
<td>36.9±4.4</td>
<td>48.7±9.0**</td>
<td>32.0</td>
</tr>
<tr>
<td>Insular cortex</td>
<td>62.9±8.7</td>
<td>67.1±9.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Thalamus</td>
<td>62.3±9.2</td>
<td>66.5±9.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Rolando area</td>
<td>55.5±7.4</td>
<td>57.3±8.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Brain stem</td>
<td>41.6±3.0</td>
<td>43.2±9.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*p<0.01 **p<0.05 Compared using a paired t-test with 8 subjects of data.
Discussion

According to the study using functional magnetic resonance imaging described by Stein in 1998, nicotine activates limbic system of the human brain and interacts with the corticolimbic dopamine system as do the other abused drugs like cocaine. The corticolimbic dopamine system, which is believed to influence leaning, memory or emotional performance, appears to be the target of nicotine. The frontal lobes are rich in dopamine. Many nicotinic receptors are present in the locus ceruleus noradrenergic neurons, which are known to the project into the forebrain and hippocampus. These locus ceruleus neurons and their projections are to regulate behavioral arousal and vigilance.

Our date support these hypothesis from the aspect of the regional cerebral blood flow.

Smoking produces a heterogeneous pattern of activation rather than homogeneous alterations in the whole brain.

The sites activated by smoking are the limbic system, frontal lobe. Activation in these structures is consistent with smoking's behavior-arousing and behavior-reinforcing properties in humans.

Smoking interacts with the corticolimbic dopamine system as do the other abused drugs.

References

Assessment of Regional Cerebral Blood Flow by Xenon-Enhanced Computed Tomography during Mastication in Humans

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Abstract. It is suggested that mastication stimulates the brain and accelerates its energy-consuming metabolism. This study was designed to determine its effects on regional cerebral blood flow (rCBF) using xenon-enhanced computed tomography (Xe-CT). Seven male volunteers, aged 24-57 years, inhaled 30% xenon in a 4 minutes wash-in and 4 minutes wash-out protocol. CT was scanned every 54.5 seconds. The subjects were instructed to chew a gum continuously at a rate of 1 bite per second except at the time of CT scanning (5.5 seconds). A second CBF was done 20 minutes later. Subtraction (mastication-baseline) maps were created. CT images were taken at three levels so as to include the cortex, basal ganglia, limbic system, brainstem and cerebellum. The results demonstrated a significant rCBF increase in the fronto-temporal cortex, caudate nucleus, thalamus and minor increase in the rolandic areas, insula, cingulate and cerebellum. Further studies are needed to validate the clinical significance of these findings.

Key words: Mastication, Xenon, Cerebral Blood Flow

Introduction

The interaction between mastication and regional cerebral blood flow (rCBF) has been previously demonstrated in experimental1,2,3 and clinical4,5,6 conditions. It is suggested that mastication stimulates the brain and accelerates its energy consuming metabolism.7 In a PET8 and MRI9 study in humans, Momose et al9 observed a widespread increase in rCBF during mastication. Despite the accuracy of PET and MRI studies, their validation is limited in routine practice by the heavy equipement required and high cost ($3-5million). Xenon-enhanced computed tomography (Xe-CT) does not involve costly site preparation. The equipement cost is less than $100,000. With it’s high spatial resolution and depth sensitivity, Xe-CT generates accurate, reproducible CBF values within a full range of flow for regional or global regions of interest. Unlike Xenon 133, inhaled xenon, used in Xe-CT, is nonradioactive (stable).

As data lacks in the literature, the present study was undertaken to determine the effects of mastication on rCBF, in humans, using Xe-CT.

Materials and Methods

After obtaining their consent, seven healthy male volunteers, aged 24-57 years, were included in the study. The inhalation protocol consisted of 30% xenon in a 4 minutes wash-in and 4 minutes wash-out protocol. CT was scanned every 54.5 seconds. With their eyes closed and their ears plugged, the participants were instructed to chew a tasteless gum continuously at the rate of one bite per second except at the time of CT scanning (5.5 seconds). They underwent two CBF measurements: baseline and during chewing 20 minutes later. CT images were taken at three levels so as to include cerebral cortex, basal ganglia and cerebellum (Figure 1). Subtraction (chewing-baseline) CBF maps were created and values were noted as mean and standard deviation. Global results were expressed as mean ± SD or percent change in CBF (CBF % change) induced by chewing.

Statistical analysis was performed by Student or Fischer’s exact test where appropriate with p < 0.05 considered as significant.

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4PET: Positron Emission Tomography

5MRI: Magnetic Resonance Imaging
Results

The study population was homogenous: 7 male adults, all right handed, with temporomandibular joint integrity. The brain scans were normal in all.

Widespread increase in rCBF was observed during mastication: significant in the fronto-temporal cortex, the caudate nucleus and thalamus and statistically not significant (NS) in the parietal cortex, insula, cingulate and cerebellum (Figure 2). CBF maps of one of the subjects are presented in Figure 3.

Discussion

The masticatory system is a coordinated function involving three units:

- peripheral effector organs (temporomandibular joint, teeth, tongue, oropharynx and craniofacial muscles)
- neural input and output pathways dominated by the trigeminal and autonomic fibers
- central nervous system: brainstem, thalamus, caudate nucleus and cortex.

Physiologically, mastication is a rhythmic act with voluntary, automatic and inhibitory components. For technical reasons, this study was designed for voluntary mastication. Generally, the presence of food in the mouth stimulates the periodontal and oropharyngeal mechnoreceptors which activates in turn the cortical and subcortical structures through specific neural pathways. The trigeminal motor nucleus controls the muscles of mastication (internal and external pterygoid, temporalis and masseter) as well as the mylohyoid, the anterior belly of the digastric, the tensor veli palatini (soft palate), and the tensor tympani. These muscles of mastication, working jointly with other muscles regulate the different jaw movements needed for chewing. The velum palatine on contraction brings the soft palate to one side and prevents food from entering the nasal pharynx. The contraction of the tensor tympanic muscle has a pulling effect on the malleus in the middle ear. This restricts the movement of the tympanic membrane to prevent damage of the inner ear on exposure to a loud noise. Other important functions of the human masticatory apparatus include swallowing, respiration, speech and posture with the involvement of facial (VII), glossopharyngeal (IX) vagus (X) and accessory (XI) nerves.

Regulation of the entire masticatory system is provided essentially by the reticular formation through the median raphe nucleus and the locus ceruleus which are respectively serotonergic and noradrenergic neurotransmitter nuclei.

Previous reports on neuropathological interaction between mastication and cerebrovascular function include: eating
epilepsia, memory loss as a result of reduced masticatory function, cerebrovascular insufficiency induced by mastication.

As a quantitative marker of cerebrovascular function, CBF evaluation represents an important pathophysiologic approach of the masticatory system. Our results corroborate previous reports, i.e. a widespread increase in CBF. However, we consider the fronto-temporal cortex, the thalamus and the caudate nucleus as specific masticatory sites for two main reasons: i) the marked CBF increase and ii) the predominant trigeminal projections in these areas especially in the ventrolateral nucleus (VLN) of the thalamus. The VLN is the principal motor relay nucleus. It projects to the primary motor complex which is responsible for initiating voluntary movements. It integrates input from basal ganglia (caudate nucleus, putamen and globus pallidus) with feed-back from the cerebellum before projecting the integrated information to the motor cortex. These voluntary masticatory messages are transmitted primarily by the mesencephalo-thalamo-cortical circuits.

The complexity of the neural input and output pathways with various interconnections may explain the widespread increase in CBF during mastication. However, our initial precautions of closing the eyes, plugging the ears and using tasteless chewing gum may have contributed in minimizing visual, auditory and gustative input participation. This was correlated with the minimal CBF increase observed in occipital cortex and insula.

By identifying essential brain structures involved in mastication, the present study provides a physiologic approach of the system. The underlying mechanisms of CBF modulation are not clearly elucidated. It probably results in cerebral vasodilation with neurogenic, myogenic or metabolic influences. In animal studies, Fukasoni et al demonstrated metabolic participation by the observed increase in cortical temperature during chewing. This was validated by Goadsby et al through stimulation of trigeminal ganglion in the cat. However, the same authors observed that stimulation of sphenopalatine ganglion increased CBF independent of metabolic activity (glucose utilization). Seylaz et al provided evidence of the significant role played, in CBF activation, by the cholinergic and vasoactive intestinal polypeptidergic innervation of the cerebral vessels arising from the sphenopalatine ganglion. These observations reveal the different mechanisms involved in CBF activation during mastication. The present study design failed to demonstrate the degree of participation of these different mechanisms.

However, as mastication was halted during CT scanning to prevent motion artifact, CBF values obtained may reflect the residual effects of the phenomenon. These residual effects may last about 15 minutes after cessation of mastication. Further studies, under pathologic conditions, are mandatory to effectively assess the clinical relevance of our findings.

This information is expected to provide further awareness on the implication of the masticatory system in certain cerebrovascular disorders for adequate patient care. Two category of patients are particularly at risk. On the one hand, those with cerebral autoregulatory limits exposed to situations involving the craniomandibular apparatus: mastication, speech, swallowing, respiration, posture, or intubation during anesthesia. On the other hand, patients with peripheral craniomandibular disorders (morphologic or functional) may be subject to cerebrovascular compromise as a result of inadequate brain analysis of the input messages from peripheral stimulation.

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