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Potential Changes with Gamma-band Oscillation at the Frontal Scalp Elicited by Intravenous Olfactory Stimulation in Humans

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Abstract

Intravenous olfaction is a unique stimulation method often used in Japan to diagnose olfactory disturbances. Odorant is injected into a vein and transported by blood flow and respiration to the upper air tract. The intravenous olfaction might allow the potential at the frontal scalp to be recorded without contamination from electromyograms, such as those caused by sniffing. We injected Alinamin (thiamine propyldisulphide) into healthy subjects according to a standard protocol for clinical intravenous olfaction testing and we simultaneously recorded potential changes at the frontal scalp. When Alinamin was injected into the right median cubital vein over a 20 s period, the potential changes with gamma-band oscillations were detected 17.6 ± 6.7 s (mean ± SD) after the start of the injection. The main frequency component of this gamma-band oscillation is 30–160 Hz. The gamma-band oscillation elicited by intravenous olfactory stimulation (VOP) was similar to the induced wave of the olfactory bulb. Mapping the VOPs on the frontal scalp of a subject with less developed frontal sinuses and the relation between the thickness of the frontal sinuses and VOP amplitude suggest an intracranial source, possibly the olfactory bulb. The gamma-band potential at the frontal scalp is a useful measure of central disturbance.

Introduction

Intravenous olfaction is a unique mode of olfactory stimulation. Odorant injected into a vein is transported via blood flow and respiration to the upper air tract. Subjects with respiratory hyposmia, not associated with olfactory neuronal hyposmia, can often perceive intravenous olfaction.

The phenomenon of intravenous olfaction, caused by the injection of neosalvasan, was discovered by Kraupa-Runk (Forcheimer, 1916). Recently, thiamine propyldisulphide (Alinamin; Takeda Chemical Industries, Osaka, Japan) has been widely used to induce intravenous olfaction. The intravenous olfaction test, or Alinamin test, is often performed in Japan to diagnose olfactory disturbances in conjunction with T&T olfactometry (Takagi, 1989). The standard protocol for the intravenous olfaction test includes measuring the latency and duration of smelling from the start of intravenous administration of Alinamin (2 ml injected in increments of 0.1 ml/s). Subjective intravenous olfaction is known to have clinical importance (Takagi, 1989). However, if the subjective response is unreliable, then the diagnostic value of the test is diminished. Therefore, an objective intravenous olfaction test is desirable.

Several non-invasive methods for measuring olfaction have been used to achieve objective olfactometry. Olfactory evoked potentials are the most popular method for this purpose (Finkenzeller, 1966; Allison and Goff, 1967; Kobal and Plattig, 1978; Auffermann *et al*., 1993); however, this test requires special olfactory stimulating equipment that must be constructed by researchers themselves. Electrical stimulation of the olfactory mucosa has also been used to produce electrical olfactory evoked potentials (EOEPs) (Ishimaru *et al*., 1997, 2002).

Gamma-band oscillation has been noted in electroencephalograms (EEGs) during experiments with EOEPs (T. Ishimaru, unpublished data). This oscillation was similar to the induced waves (IWs) of the olfactory bulb recorded in animals (Adrian, 1942, 1950, 1953; Ottoson, 1954, 1959a,b; Yamamoto and Yamamoto, 1961; Bresseler and Freeman, 1980; Dorries and Kauer, 2000) and humans (Sem-Jacobsen *et al*., 1953; Hughes *et al*., 1969). Therefore, we thought that human IWs should be detectable at the scalp. The aim of the present study was to measure and analyze intravenously activated IWs as EEG oscillations.

Subjects and methods

Eleven healthy subjects, eight males and three females, with normal olfaction (ages 25.5 ± 2.6, mean ± SD) were

examined. In addition, seven subjects (age 53.9 ± 15.1, mean ± SD), four males and three females, with chronic sinusitis but normal or nearly normal intravenous olfaction were examined because the sizes of their frontal sinuses were measured by pre-performed computer tomography and /or X-ray photographic examination for sinus surgery. Olfactory abilities were measured by T&T olfactometry and cognitive olfactory threshold levels that were 1.0 or lower were regarded as normal. The detection threshold of the subjects with chronic sinusitis was 3.7 ± 2.9 (mean ± SD). All subjects understood the aim of the study and gave their informed consent. All experimental procedures followed the World Medical Association Declaration of Helsinki Recommendations guiding physicians in biomedical research involving human subjects.

A pair of electrodes was positioned on the center of the frontal scalp superior to the orbits for bipolar recording. The distance between the recording electrodes was ~4.5 cm. This location is well-suited for recording presumed olfactory bulbar potentials, EOEPs, as reported previously (Ishimaru *et al.*, 1997, 2002). An additional two pairs of recording electrodes were positioned on bilateral sides of the frontal scalp of one of the hyposmic subjects with chronic sinusitis. The frontal center scalp was connected to a ground (Figure 1). The potential at the frequency band of 1–500 Hz was amplified (100 dB) using a biophysiological oscilloscope (Neuropack MEB-5500, Nihon-Khoden, Tokyo, Japan) and converted from analog to digital (A/D) signals using a 2000 Hz sampling clock and 12 bit resolution (PCI-6023, National Instruments, TX, USA). Anti-alias low-pass filters were inserted between the biophysiological oscilloscope and the A/D converter to attenuate potential signals above 500 Hz. Potential data were saved on a hard disk and magneto-optical disks (MO) of a personal computer, and processed offline using a 30–200 Hz digital Butterworth bandpass filter (24dB/octave), except for the data used for the frequency analysis. The computer applications used were developed using LabVIEW 5.1J (National Instruments).

The subjects were instructed to push a hand switch when they perceived intravenous olfaction. This event was labeled the subjective response (SR). The SR signal was captured via the A/D converter along with the potentials and stored on the personal computer. If the duration of the SR exceeded 240 s, it was regarded as 240 s (maximum).

Alinamin (2 ml i.v.) was administered as an intravenous odorant, injected into the right median cubital vein over a period of 20 s according to the standard protocol of the intravenous olfaction test (Takagi, 1989). Physiological saline was administered to three healthy subjects under the same protocol as Alinamin administration. A control group of eight healthy subjects underwent needle insertion with no administration of any substance. Administrations were performed in the order: control, physiological saline, Alinamin.

Potentials were recorded for a total of 300 s, starting from 60 s prior to, until 240 s following the onset of the administration, labeled from –60 s to +240 s. The injection of Alinamin began at time 0 s. The subjects kept their eyes open, but wore eye masks to eliminate the influence of visual cues, and their ears were covered with headsets to avoid auditory cues.

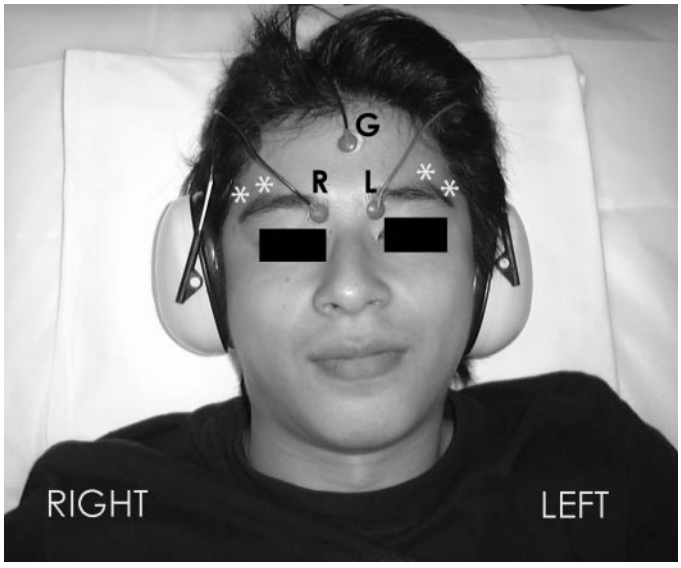

Figure 1 Location of recording electrodes. Recording electrodes were located at the medial end of both orbits as bipolar conductors. Right (R) and left (L) electrodes were connected to inverted and non-inverted inputs of the amplifier respectively. The center of the frontal scalp was led to a ground (G). Additional recording electrodes (*) were used for recording potential from bilateral sides of the frontal scalp.

The amplitude response was calculated from rectified potential traces averaged over 1 s windows. A 0.1 Hz Bessel low-pass filter was utilized to smooth this amplitude, creating a smoothed pseudo-DC response. Every pseudo-DC response was normalized against the amplitude of the mean pseudo-DC response over the period –60 s to –50 s. The mean normalized pseudo-DC response from all subjects was labeled MPDC.

A fast Fourier transform (FFT) with a Hanning window was employed for frequency analysis. Potentials were transformed to time-related frequency power spectra (TRFS). The short-time Fourier transform (STFT) algorithm from the LabVIEW signal-processing package (National Instruments) was used for this purpose.

The thickness of the frontal sinus was measured by the computed tomographs (CTs) prepared for sinus surgery in seven subjects. Because the frontal sinus was shown in several slices of the CT, the slice with the deepest frontal sinus was chosen for measurement and regarded as the thickness of the frontal sinus, from which the sum total of the thickness of right and left frontal sinuses was calculated. The subjects had chronic sinusitis, but they did not have polyps in the frontal sinuses.

Results

Potential oscillation elicited by Alinamin injection and physiological saline control

Potential oscillations appeared after the start of Alinamin administration. These responses were labeled intravenous olfaction-elicited potential (VOP). The amplitude of these oscillations observed during the SR period was remarkable. VOP was observed in all healthy subjects, and all healthy subjects perceived a garlic-like smell with a mean latency (SR latency) of 17.6 ± 6.7 s after the Alinamin injection. SR exhibited a mean duration of 135.8 ± 53.8 s after the injection of Alinamin. The subjects with chronic sinusitis also perceived a garlic-like smell and VOP was observed.

The VOP of a 22-year-old female (Figure 2) typifies the responses displayed by subjects: a burst-like oscillation was observed following the Alinamin injection. VOPs were not observed when nothing (n = 8) or saline (n = 3) was injected.

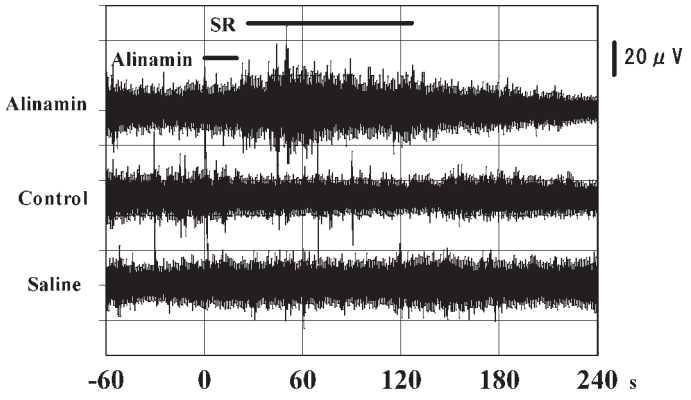

Figure 2 Potentials elicited by Alinamin or physiological saline, and in the control state. Potential recorded before and after injection of Alinamin or physiological saline (saline) and without injection (control) from a single subject. Intravenous olfaction SR occurred at 27 s and disappeared at 127 s after stimulation. Time courses of Alinamin injection and SR are indicated as bars above the potential waveforms. Time 0 s indicates the start of administration.

Frequency band analysis of VOPs elicited by Alinamin injection in healthy subjects

The amplitude of VOPs increased while subjects perceived the garlic-like smell of Alinamin (Figure 3, 25-year-old male). VOPs were analyzed using digital filter banks equivalent to four-pole Butterworth filters. VOPs were observed within the gamma-band of 30–200 Hz, and very little or no responses were observed in the range below 30 Hz. Some remarkable activity was noted over the 200–500 Hz range.

MPDC elicited by Alinamin injection and control in healthy subjects

During the pre-stimulation period from –60 s to 0 s, the MPDC was 0.98 ± 0.21 times as large as the baseline activity. At the beginning of Alinamin administration (0 s), the MPDC was 1.05 ± 0.31 times as large as the baseline activity. After the injection, the MPDC increased up to a maximum of 1.81 ± 1.00 times as large as the baseline activity. The increase in the MPDC became statistically significant at +14 s (t-test, $P < 0.01$, Figure 4a).

For eight of the 11 healthy subjects, potentials without the injection were recorded as control potential (CP); five for 180 s and three for 300 s. Then, data from –60 to +120 s were analyzed. As with the VOPs, CP amplitude in the frequency-band ranging from 30 to 200 Hz was averaged and analyzed using the same protocol as for MPDC. This was called the control MPDC. The ratio of the magnitude of control MPDC expressed in the relative magnitude to the baseline activity displayed no statistically significant variations (t-test, $P > 0.01$) before +70 s after the onset of pseudo-stimulation (Figure 4b).

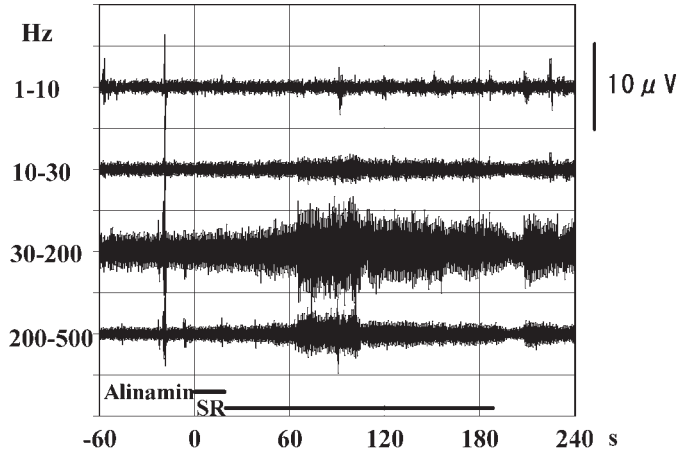

Figure 3 Potential oscillation recorded from one subject. The potential was digitally filtered to four frequency bands. The injection of Alinamin was started at time 0 s and continued till 20 s. Intravenous olfaction SR occurred at 18 s and disappeared at 190 s. Time courses of Alinamin injection and SR are indicated as bars below the potential waveforms.

Latencies of SR and VOP in healthy subjects

The mean onset latency of the SR was 18.3 ± 6.6 s, where that of the VOP was 17.6 ± 6.7 s. When the SR latency was shorter, the VOP tended to be shorter. In Figure 5, the SR latency was plotted against the VOP latency, and the correlation between mean SR latency (18.3 ± 6.6 s,) and mean VOP latency (17.6 ± 6.7 s) was significant (r = 0.741, n = 11, $P < 0.01$, Student's t-test). The difference in latency between the mean SR and mean VOP was not significant (0.6 ±4.8 s, n = 11, $P > 0.05$, paired t-test)

Frequency analysis in healthy subjects

TRFS from all healthy subjects were averaged (Figure 6).

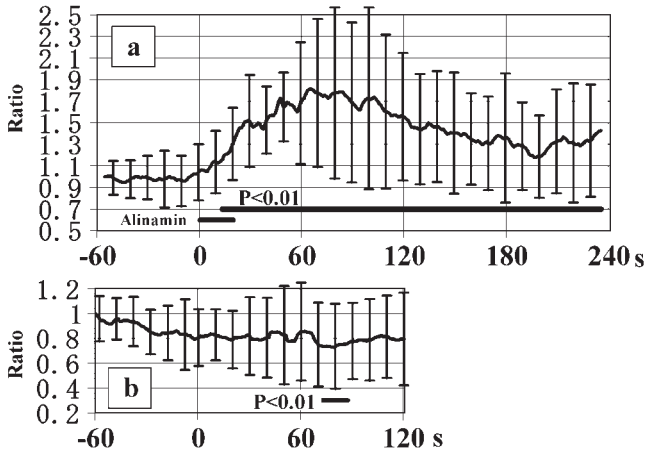

Figure 4 Mean normalized pseudo-DC response (MPDC) elicited by Alinamin injection **(a)** and control **(b)**. (a) Normalized VOP amplitude responses (pseudo-DC response) of 11 subjects were averaged. Vertical bars indicate SD. Before averaging, every VOP amplitude response was normalized to a value representing the mean amplitude from –60 to –50 s for every subject. Significant increase in the MPDC after Alinamin injection was indicated as a horizontal bar below the MPDC. Injection of Alinamin was also indicated as a horizontal bar. (b) Pseudo-DC responses of eight subjects were averaged for the controls according to the same protocol used in (a). There was no significant change other than for the period from 0 to 70 s.

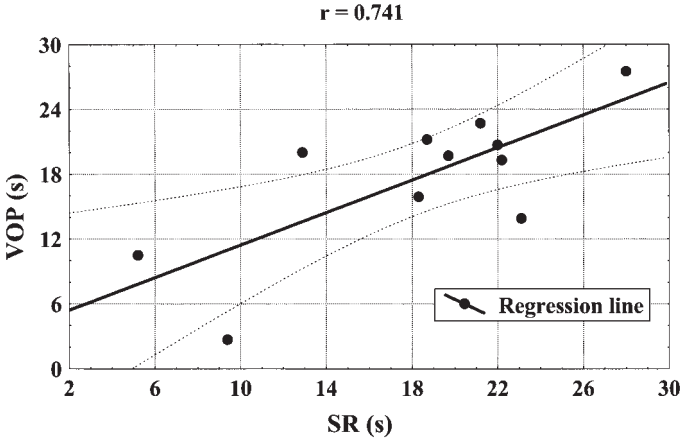

Figure 5 Correlation between the latency of SR and VOP. The VOP latency is plotted against the SR latency. The correlation coefficient (*r*) between the SR latency and VOP was 0.741 ($P < 0.01$, $n = 11$ Student's *t*-test). Solid and broken lines indicate a regression line and 95% confidence region respectively.

The main component of the TRFS, between 30 and 160 Hz, appeared after the intravenous injection of Alinamin. The frequency spectrum extended to 260 Hz at 50 s after the injection. Low signal levels were observed between 10 and 30 Hz.

Localization of VOP

To locate the possible source of the VOP, pairs of recording electrodes were placed at three sites (left, center and right;

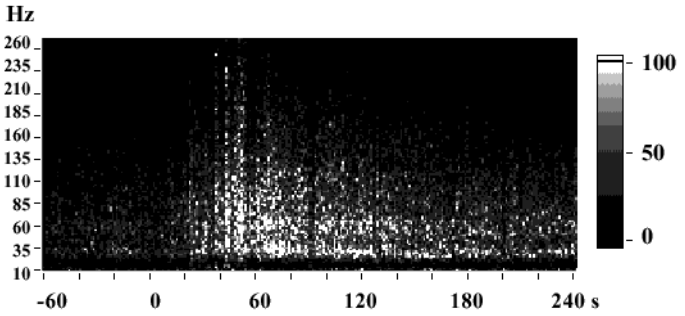

Figure 6 Averaged frequency spectrums of potential oscillation. Time-related frequency spectra (TRFS) were averaged ($n = 11$). Alinamin was injected in the period 0 to 20 s. Gray scale indicates relative intensity of TRFS.

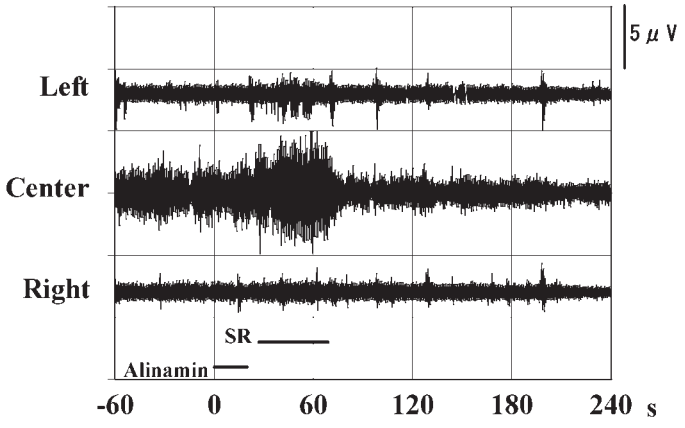

Figure 7 Changes in the VOP according to recording location on the frontal scalp. VOPs were recorded at the central, right and left parts of the frontal scalp in a subject with less-developed frontal sinuses. Remarkable VOP oscillation was observed at the center of the frontal scalp, but small potentials were noted at the right or left side of the frontal scalp.

see Figure 1) on a patient suffering from chronic sinusitis with respiratory hyposmia who had less developed frontal sinuses. The frontal sinuses of this subject were found to be extremely small on X-ray examination. The largest amplitude of VOP after the Alinamin injection was recorded at the center of the frontal scalp. The latency and duration of SR were 26 and 43 s respectively. However, no remarkable VOP oscillation was observed on either the right or left side of the frontal scalp (Figure 7).

VOP and the thickness of the frontal sinus

The correlation between the thickness of the frontal sinus and the maximum amplitude of the VOP was investigated in subjects with chronic sinusitis ($n = 7$). The maximum amplitude of the VOP had a significance inversely related to the sum total of thickness of the right and left frontal sinuses ($r = –0.859$, $P < 0.02$, Student's *t*-test, Figure 8).

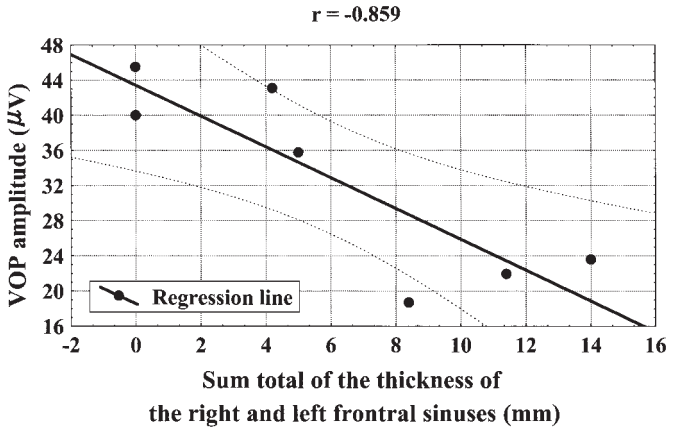

Figure 8 Correlation between the maximum amplitude of VOP and the thickness of the frontal sinuses. The maximum amplitude of VOP (VOP amplitude) is plotted against the sum total of the thickness of the right and left frontal sinuses. Correlation coefficient (r) between the maximum amplitude of VOP and the total thickness of the right and left frontal sinuses was –0.859 ($P < 0.02$, $n = 7$, Student's t-test). Solid and broken lines indicate a regression line and 95% confidence range respectively.

Effects of pain from the Alinamin injection and possible electromyogram contamination

Administration of Alinamin caused varying degrees of intravascular pain at the injection site. Two subjects reported severe pain, whereas others reported only slight or no pain. Seven subjects with chronic sinusitis did not feel pain; one of the seven subjects who participated in the three-channel potential recording (see Figure 7) did not feel pain. VOPs were observed in subjects irrespective of reported sensations of pain. No overt signs of pain, such as wrinkling of the forehead, were observed in any of the 11 healthy subjects and seven subjects with chronic sinusitis. To distinguish contamination of the potentials by electromyographic signals from facial muscles, three healthy subjects were instructed to wrinkle the middle of their foreheads. When they did so, the amplifier was saturated by the high-voltage electromyogram from the facial muscles.

Discussion

The source of the VOP

A pair of recording electrodes was positioned just above the medial end of the orbits ~4.5 cm apart. Olfactory bulbar potentials were suspected when they were recorded at a similar position, though the electrodes had previously been placed above the eyebrows (Ishimaru *et al*., 1997, 2002). As VOPs in the present study were recorded according to the bipolar recording method, the origin of gamma-band VOP was suspected to be located near the orbits. The main source of VOP on the frontal scalp has not been clearly identified. It is known that potential change in the retina is detectable from electrodes placed on the bridge of the nose between the eyes (Harden, 1974). The frequency of the electro-oculogram was <30 Hz; all components of the electro-oculogram were rejected by a band-pass filter (30–200 Hz, 24dB/octave). Therefore, there was no possibility of contamination by the electro-oculogram.

If VOPs originate from intracranial tissue, the size of the frontal sinus would influence the magnitude of VOPs. In the present study, we fortunately encountered a subject with less-developed frontal sinuses, and roughly mapped the VOPs on the frontal scalp by placing multiple recording electrodes. The VOP was highest on the center of the frontal scalp, but nothing was detected on the lateral sides. Furthermore, the thickness of the frontal sinuses inversely affected the amplitude of the VOPs. These findings indicate the possible origin of VOP is at the intracranial tissue behind the center of the frontal scalp.

The frontal cortex, piriform cortex and olfactory bulb were suspected to be the origin of this gamma-band oscillation since they receive olfactory projection. However, so far there has been no report on olfactory gamma-band oscillations in the frontal cortex. The piriform cortex seems too deeply located to contribute to the VOPs. The distance between the orbit and the piriform cortex is also longer than the distance between the orbit and the olfactory bulb. Therefore, the olfactory bulb might be the most probable origin of the gamma-band potential. Direct intracranial potential recording from the olfactory bulb is probably required to locate the origin, but this cannot be determined in human studies for ethical reasons. It is generally known that olfactory bulb activity produces gamma-band IW oscillations when the olfactory nerve is stimulated in vertebrates such as frogs (Ottoson, 1959b), and rabbits (Ottoson, 1954, 1959a; Bressler and Freeman, 1980; Yamamoto and Yamamoto, 1961). Human gamma-band IW oscillations produced by odorant stimulation have been noted in recordings made during neurosurgery (Sem-Jacobsen *et al*., 1953; Hughes *et al*., 1969). Furthermore, IW was observed in the rabbit olfactory bulb when Alinamin was injected into a vein (Uemura *et al*., 1957).

The injection of Alinamin often causes pain. Somatic stimulation to the median nerve evokes gamma-band oscillation of the EEG (Pantev, 1995; Hashimoto *et al*., 1996). The source of somatic EEG oscillation is the somatosensory cortex in the contralateral hemisphere. VOPs were recorded from the frontal scalp, but not from the lateral scalp located nearer to the somatosensory cortex. Recordings of the VOPs from the right, center and left parts of the frontal scalp also indicated that the highest amplitude of VOP was detected in the front center of the frontal scalp (Figure 7). The frequency spectra peaks of somatic EEG oscillations are reported for 40 and 600 Hz. As oscillation frequency bands >500 Hz were cut by low-pass filters in the present study, the 600 Hz EEG was not recorded. Although the VOP appears to contain the intravenous olfactory response, it is difficult to deny the possible contamination of the 40 Hz EEG by pain. The contamination of the EEG by pain possibly aug-

mented the standard definitions of MPDC after Alinamin injection.

Visual and auditory cortices also showed oscillating gamma-band EEGs (Pantev, 1995). Since the eyes and ears were masked in the present study, contamination by auditory and/or visual EEGs was unlikely. We hypothesize that most of the components of the VOP were derived from the IW.

The significant correlation observed for the latencies of the VOP and the SR support the hypothesis that the VOP is an olfactory-related response.

The nature of VOPs

The main frequency of VOPs in the spectrum is >30 Hz as the IW frequency band in the olfactory bulb. The IW frequency ranges from 35 to 85 Hz in mammals (Bressler and Freeman, 1980). Most reports concerning IW frequency appear to have referred directly to the waveform in the oscillograph. Therefore, it is considered that the overtone of the IW might have been overlooked in previous studies. The VOP had a wide frequency spectrum (30–200 Hz) in the present study; a more restricted range (35–85 Hz) was used in previous studies (Bressler and Freeman, 1980). However, there is no contradiction between the two findings because the base frequency band was ~30 Hz in the present study, and base frequency should be identical to that in the classical IW measured from wave cycles on the oscillograph. Hughes *et al*. (Hughes *et al.*, 1969) measured frequency spectrums of human IW using a heterodyne wave analyzer and reported that the human IW ranged from 20 to 70 Hz. VOPs contained frequency spectrums >70 Hz in the present study. The recent finding that olfactory EEG oscillation had a wide frequency spectrum in the rat (Hirano *et al*., 1999) also supports the present hypothesis that the IW has a wide frequency spectrum. The difference between human IW and VOP could be due to the difference in frequency spectrum of the background noise between the tube amplifier used in 1969 and the solid-state amplifier used in 2000.

The changed ratio of control MPDCs displayed minor variations without intravenous stimulation (Figure 4b), except for variations after +70 s. In other words, no significant changes occurred in the gamma-oscillating potentials until +70 s after pseudo-stimulation. Alinamin administration increased MPDC significantly (*t*-test, $P < 0.01$) at +14 s, and the VOP thus elicited are therefore considered to be statistically reliable.

The SR occurred at +18.3 ± 6.6 s, in spite of the fact that the normal value was +8.0 ± 0.5 s in the previous study (Takagi, 1989). The respiratory cycle was fixed to 2 s in the previous study but unrestricted in the present study. The reason for the longer SR latency might be that the respiratory cycle was longer than 2 s in the present study. The VOP increased significantly at +14 s in the MPDC (Figure 4). A 4 s difference therefore existed between the SR and VOP latency. However, SR latency was 3.3 s shorter than VOP in the regression line (Figure 5). Mean SR latency was 0.6 ± 4.8 s (mean ± SD) longer than VOP. Differences in the latencies between SR and VOP were attributed to the influence of background EEG rather than variations in the reaction times of subjects.

VOP was recorded until +240 s after stimulation and a significant MPDC was obtained at +14 s. The significant VOP therefore lasted for longer than 226 s, but the SR continued for 135.1 ± 53.8 s, shorter than the VOP.

Although the potentials displayed variations without olfactory stimulation, they were stable for 130 s. Control potentials did not significantly change until +70 s after pseudo-stimulation. If significant, the increases in amplitude of VOP observed after +70 s may have represented basal changes in the potential. Injection of saline did not elicit a VOP. Furthermore, intravenous injection itself did not elicit a VOP nor did it elicit any artifacts.

Conclusion

Gamma-band oscillations elicited by intravenous olfactory stimulation detected from the scalp seem to have possible applications as an objective olfaction test, and offer a method for studying human olfaction.

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