Inhibition by Intravenously Administered Sodium Bicarbonate of Neuronal Activity in Medial Vestibular Nucleus Neurons

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Abstract—The effects of 7% sodium bicarbonate on medial vestibular nucleus (MVN) neurons were examined to elucidate the mechanism underlying its anti-vertigo action, using α-chloralose-anesthetized cats. Intravenous injection of the drug at 1, 2 and 4 ml/kg every 10 min dose-dependently inhibited rotation- and glutamate-induced firing of type I neurons, although a low dose of the drug enhanced firing in a few neurons. However, microiontophoretic application of bicarbonate ions did not inhibit rotation- or glutamate-induced firing. After injection of the drug, the $P_O_2$ level in arterial blood did not differ from previous levels, but the bicarbonate ion levels dose-dependently increased concomitantly with an increase in pH, as compared with previous levels. These results suggest that the intravenous injection of 7% sodium bicarbonate directly inhibits the neuronal activity of the MVN, although the lower dose may enhance neuronal activity by acting on the peripheral vestibule.

Solution containing 7% sodium bicarbonate has been widely used for the treatment of vertigo common in such diseases as Ménérie’s disease (1, 2). The effects of this drug on such conditions of vertigo are believed to be due to the reduction of lymph hydrops in the semicircular canals of the inner ear or due to the degradation of blood sludge in the peripheral capillaries in the labyrinth. However, it remains unknown whether or not this drug directly or indirectly affects the neuronal activity of the vestibular nucleus which receives input from the peripheral vestibule. Therefore, an electrophysiological study was performed to elucidate the mechanism underlying the therapeutic effects of this drug on vertigo.

Materials and Methods

Electrophysiological study: Fifteen adult cats weighing 3.3–5.2 kg were used. Under ether anesthesia, the trachea and femoral veins were cannulated. Then, the ether anesthesia was replaced with α-chloralose (30–40 mg/kg, i.v.), with supplemental doses at 10 mg/kg (i.v.) as required. The animal was fixed in a stereotaxic apparatus with its head inclined 15° nose-down to isolate optimally horizontal canal responses. All wound edges and pressure points were locally anesthetized with 8% lidocaine repeatedly throughout the experiment. Body temperature was maintained at 36.5–37.5°C with a heating pad. The animal was placed on a turntable that was manually rotated sinusoidally in a horizontal plane at an angular velocity of approximately 60°/sec for 120°. Neuronal activities in the MVN (P: 8–8.5, L: 2.5–3.0, H: −3 to −3.5) (3) were extracellularly recorded using a glass-insulated silver wire microelectrode (electrical resistance: approx. 1 MΩ) attached along a seven-barrelled micropipette (outer diameter: approx. 10 μm). The neuronal activities were displayed on an oscilloscope (Nihon Kohden, VC-11) and recorded on a recticorder (Nihon Kohden, RJG-4124) via a spike counter (DIA Medical System, DSE-235P). Each pipette was filled with 1 M sodium bicarbonate, 1 M monosodium L-glutamate and 2 M NaCl. These chemicals were microiontophoretically given, as anions,
in the immediate vicinity of the target neuron recorded using an iontophoresis programmer (WP-I, model 160). In addition, 7% sodium bicarbonate at 1, 2 and 4 ml/kg was intravenously injected every 10 min. The means of the maximum firing rates were obtained from the last five trials out of 6 rotations, to avoid the fluctuation of the angular velocity in the beginning of the rotation. The statistical significance between the means before and after injection of 7% sodium bicarbonate or during iontophoretic application of bicarbonate ion in each neuron was determined using Student's t-test. Then, the mean of the maximum firing rate following application of the drug was expressed as a percentage of that before drug administration. The statistical significance between the means of the percentage in all neurons tested before and after drug application was also determined by the unpaired Student's t-test.

At the termination of each experiment, the recording site was marked by passing a direct current of 20 μA for 10–20 sec through the electrode and histologically checked by staining with cresyl violet. Further details of the experimental procedures have been described elsewhere (4). Blood analysis: Arterial blood was collected in 4 animals which had operations similar to the electrophysiological studies 2, 5 and 10 min after intravenous injection (interval: 10 min) of 7% sodium bicarbonate at doses of 1, 2 and 4 ml/kg. Then, $P_{O_2}$, $P_{CO_2}$, pH and $HCO_3^-$ levels in the blood were measured using a standard blood gas analyzer (Chiba-Corning, model 170).

**Results**

Effect of intravenous application of sodium bicarbonate: Out of 169 neurons recorded, 156 neurons were histologically found in the MVN. The MVN neurons have been classified into four types, according to their responses to the horizontal, sinusoidal rotation of the animal as described by Duensing and Schaefer (5). Briefly, type I neurons exhibited an increase and a decrease in firing with a horizontal rotation in the direction ipsilateral and contralateral to the recording site.

![Fig. 1. Effects of intravenous application of 7% sodium bicarbonate on rotation- and glutamate-induced firing of type I medial vestibular nucleus neurons.](image-url)
Table 1. Effects of intravenous application of 7% sodium bicarbonate on rotation- (A) and glutamate- (B) induced firing of medial vestibular nucleus neuron

| No. | A. Rotation-induced firing | B. Glutamate-induced firing |
|-----|----------------------------|-----------------------------|
|     | Control<sup>a</sup> (spikes/sec) | 1 ml/kg (%) | 2 ml/kg (%) | 4 ml/kg (%) | 20 min<sup>c</sup> (%) | Control<sup>b</sup> (spikes/sec) | 1 ml/kg (%) | 2 ml/kg (%) | 4 ml/kg (%) | 20 min<sup>c</sup> (%) |
| 1   | 154.8                       | 98.2                        | 102.6                    | 60.7                    | 59.8                    | 267.9                        | 103.9                    | 100.0                    | 65.4                    | 80.7                    |
| 2   | 84.6                        | 100.6                       | 85.4<sup>*</sup>           | 78.8<sup>*</sup>         | 61.8<sup>*</sup>         | 106.7                        | 109.4                    | 18.7                     | 0.0                     | 12.5                    |
| 3   | 132.0                       | 80.6<sup>–</sup>            | 17.2<sup>–</sup>           | 0.0<sup>–</sup>          | 3.0<sup>–</sup>          | 61.0                        | 60.0                     | 41.8                     | 11.5                    | 56.2                    |
| 4   | 40.4                        | 104.0                       | 147.8<sup>*</sup>          | 0.0<sup>–</sup>          | 4.2<sup>–</sup>          | 203.3                        | 145.1                    | 109.5                    | 9.7                     | 33.7                    |
| 5   | 53.0                        | 182.6<sup>*</sup>           | 139.1<sup>*</sup>          | 27.0<sup>–</sup>         | 65.7<sup>–</sup>         | 131.5                        | 84.0                     | 24.0                     | 36.0                    | 100.0<sup>*</sup>        |
| 6   | 103.6                       | 93.0                        | 35.5<sup>–</sup>           | 108.7                   | 96.4                    | 50.0                        | 90.0                     | 15.0                     | 20.0                    | 7.6                     |
| 7   | 35.0                        | 62.9<sup>–</sup>            | 55.7<sup>–</sup>           | 5.7<sup>–</sup>          | 8.0<sup>–</sup>          | 27.5                        | 200.0                    | 345.5                    | 0.0                     | 254.5                   |
| 8   | 89.0                        | 97.2                        | 76.7<sup>–</sup>           | 14.0<sup>–</sup>         | 36.5<sup>–</sup>         | 121.1                        | 113.2                    | 93.4                     | 20.4<sup>–</sup>         | 74.2                    |
| mean | 86.2                       | 99.9                        | 82.5                     | 36.9<sup>–</sup>         | 41.9<sup>–</sup>         | 121.1                        | 113.2                    | 93.4                     | 20.4<sup>–</sup>         | 74.2                    |
| S.E. | 15.2                       | 13.2                        | 16.4                     | 14.5                     | 12.2                    | 33.1                        | 17.5                     | 44.5                     | 8.9                     | 37.8                    |

<sup>a</sup>: Mean of maximum firing rate/sec induced by rotation.  
<sup>b</sup>: Mean of maximum firing rate/sec induced by iontophoretic application of glutamate at a dose of 50 nA.  
<sup>c</sup>: 20 min after injection of the drug at a dose of 4 ml/kg.  
<sup>*</sup>: Obtained 40 min after injection of 4 ml/kg and the value is not included in the mean value.  
<sup>–</sup>: Significantly (P<0.01) increased and decreased, compared with the respective control, respectively. Values except the control are represented as a percentage of the respective control.
whereas type II neurons showed the opposite responses to the ipsilateral and contralateral rotations, respectively. Type III and IV neurons exhibited only an increase and a decrease in firing with sinusoidal rotation, respectively. In the present study, 38, 45 and 2 out of the 156 neurons were classified as type I, II and IV neurons, respectively; and the remaining 71 neurons showed no responses to horizontal rotation. Type I neurons receiving input from the labyrinths project to the contralateral abducens nucleus. Type II neurons are activated from the axon collaterals of type I neurons located on the contralateral site, and they inhibit type I neurons on the ipsilateral site (5). Therefore, to assess the drug action on the main pathway from the labyrinth to the MVN, the effects of 7% sodium bicarbonate were examined on 19 of the 38 type I neurons. The remaining 19 neurons were excluded from the results, since they were injured during the course of the experiment.

When 1, 2 and 4 ml/kg of 7% sodium bicarbonate was intravenously injected to 8 animals every 10 min, the increase in rotation-induced firing was dose-dependently inhibited in 2, 5 and 6 neurons, respectively (Fig. 1A and Table 1A). Transient enhancements of the rotation-induced increase in firing were observed in 1 and 2 neurons, although not in the remaining 5 and 1 neurons, with the lower dose at 1 and 2 ml/kg, respectively (Fig. 1B and Table 1A). The mean of the maximum firing rate induced by ipsilateral rotation in 8 neurons was significantly (P<0.01) reduced, compared with its respective control 10 min after injection of the drug at a dose of 4 ml/kg (Table 1A).

The increase in firing induced by iontophoretic application of glutamate up to 50 nA was also decreased to less than 50% of the control in 4 and 6 of the 7 neurons, 10 min after the intravenous injection of 7% sodium bicarbonate at doses of 2 and 4 ml/kg, respectively, although 1 ml/kg of the drug did not affect the glutamate-induced firing in any of the 8 neurons (Fig. 1 and Table 1B).

When bicarbonate ions were microiontophoretically applied to 11 type I neurons, the increase in firing with the ipsilateral rotation was unaffected in 8, although 2 and 1 neurons showed enhancement and inhibition, respectively, by applying a current up to 200 nA. The means of the rotation- and glutamate-induced maximum firing rate in the 11 neurons were not significantly affected during the microiontophoretic application of bicarbonate up to 200 nA. Likewise, there were no alterations of the glutamate-induced firing with iontophoretically applied bicarbonate in 10 of 11 neurons, although one neuron showed an increase in the firing. The mean of the glutamate-induced firing was not significantly affected by bicarbonate up to 200 nA (Fig. 2 and Table 2).

**Blood gases examination:** The mean Po₂ in arterial blood was not significantly altered following the intravenous injection of 7% sodium bicarbonate at doses of 1, 2 and 4 ml/kg, compared with previous levels before in-

![Fig. 2. Effects of iontophoretic application of 1 M sodium bicarbonate on rotation- and glutamate-induced firing of type I medial vestibular nucleus neurons.](image-url)
### Table 2. Effects of iontophoretic application of sodium bicarbonate on rotation- (A) and glutamate- (B) induced firing of medial vestibular nucleus neuron

| No. | A. Rotation-induced firing | B. Glutamate induced firing |
|-----|----------------------------|-----------------------------|
|     | Control<sup>a</sup> (spikes/sec) | 100 nA (%) | 200 nA (%) | Recovery<sup>c</sup> (%) | Control<sup>b</sup> (spikes/sec) | 100 nA (%) | 200 nA (%) | Recovery<sup>c</sup> (%) |
| 1   | 61.9 | 129.2<sup>*</sup> | 163.9<sup>*</sup> | 133.0 | 138.0 | 93.1 | 204.4 | 81.2 |
| 2   | 81.4 | 87.7 | 88.3 | 90.7 | 85.7 | 100.0 | 111.1 |
| 3   | 97.6 | 87.6 | 88.7 | 90.7 | 123.8 | 71.2 | 95.2 | 180.7 |
| 4   | 32.7 | 132.7<sup>*</sup> | 105.8 | 70.8 | 113.7 | 128.0 | 113.7 |
| 5   | 83.9 | 103.0 | 110.3 | 89.6 | 120.0 | 106.3 | 106.3 | 141.7 |
| 6   | 96.5 | 59.1<sup>−</sup> | 39.3<sup>−</sup> | 71.5 | 37.5 | 136.8 | 100.0 |
| 7   | 34.0 | 113.2 | 95.5 | 92.6 | 27.5 | 118.2 | 100.0 |
| 8   | 81.0 | 100.6 | 104.4 | 107.4 | 100.0 | 100.0 | 100.0 |
| 9   | 61.3 | 102.0 | 104.2 | 91.4 | 27.5 | 81.8 | 123.2 | 86.4 |
| 10  | 20.3 | 109.9 | 102.2 | 106.4 | 75.0 | 110.0 | 93.9 | 113.3 |
| 11  | 91.5 | 100.5 | 105.3 | 110.4 | 78.6 | 105.6 | 116.9 | 109.6 |
| mean | 67.5 | 103.8 | 100.2 | 98.7 | 78.6 | 105.6 | 116.9 | 109.6 |
| S.E. | 8.3 | 6.6 | 9.6 | 4.8 | 11.7 | 6.3 | 10.4 | 10.3 |

<sup>a,b</sup>: The same as described in Table 1.  <sup>c</sup>: 3 min after cessation of the drug administration.  <sup>∗</sup>: Significantly (P<0.01) increased and decreased, compared with the respective control, respectively. Values except the control are represented as a percentage of the respective control.
Fig. 3. Effects of intravenous application of 7% sodium bicarbonate on $PO_2$ and $PCO_2$ (A) and $HCO_3^-$ and pH (B) in arterial blood. Each value represents the mean±S.E. (whisker). *, **: $P<0.05$, ***: $P<0.01$: Statistically significant difference from the respective controls.

Injection. $PCO_2$ did not significantly change after injection of the drug up to 2 ml/kg, but temporarily increased 2–10 min after injection of 4 ml/kg, and then returned to the previous levels (Fig. 3A). However, the bicarbonate ionic level dose-dependently increased comitantly with an increase in pH after injection of the drug at doses of 1, 2 and 4 ml/kg (Fig. 3B).

Discussion

A low dose of 7% sodium bicarbonate (1 and 2 ml/kg), which was intravenously given to the animals, produced enhancements of rotation-induced increases in firing in a few neurons, with negligible effects on glutamate-induced firing. Therefore, the low dose may have acted on the peripheral vestibule organ to induce a vasodilatation and a decrease in blood viscosity, as reported by Hasegawa (2). However, a relatively high dose of sodium bicarbonate inhibited both rotation- and glutamate-induced firing, suggesting that the drug directly inhibited neuronal activity. This effect was not due to hypoxia, because $PO_2$ levels in the arterial blood 10 min after intravenous injections of sodium bicarbonate were not different from previous levels. In contrast, bicarbonate ionic levels were dose-dependently elevated concomitantly with increases in pH, as compared with previous levels. However, iontophoretically applied bicarbonate ions did not inhibit rotation- and glutamate-induced firing. Therefore, the higher level of bicarbonate ions in arterial blood itself is not considered to be responsible for the inhibition by intravenously applied sodium bicarbonate of neuronal activity, but may indirectly be involved in inhibition via some metabolic changes or via effects on some other neuronal activities. $PCO_2$ levels also increased 2–10 min after injection at 4 ml/kg; however, this is not considered to be responsible for the drug action, since the levels returned to the control level 20 min after the drug administration, when the inhibition of the rotation- and glutamate-induced firing was still observed.

Although the detailed mechanism underlying the antivertigo effects still remains unclear, it is noteworthy that the intravenous injection of sodium bicarbonate directly inhibited the neuronal activity of the MVN, since the drug was believed to act on the peripheral vestibule.

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