Effect of Minaprine on Changes in Monoamine Contents in Mongolian Gerbils with 5-Min Occlusion of Common Carotid Arteries

Hiroaki ARAKI, Yoshimi UCHIYAMA-TSUYUKI, Yasuko KARASAWA and Hironaka AIHARA

Department of Pharmacology, Research Center, Taisho Pharmaceutical Co., Ltd., Yoshino-cho 1-403, Ohmiya, Saitama 330, Japan

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Abstract—Effects of minaprine, a psychotropic drug, on changes in monoamines and their metabolites were examined in Mongolian gerbils with 5-min occlusion of the common carotid arteries. Noradrenaline (NA), dopamine, serotonin (5-HT), 5-hydroxyindol acetic acid, homovanillic acid and 3,4-dihydroxyphenyl acetic acid contents in the cortex, hippocampus and striatum remained unaltered during a 5-min occlusion. NA levels in the cortex, hippocampus and striatum and 5-HT levels in the hippocampus and striatum significantly decreased 30 min–2 hr after re-circulation. Particularly, minaprine significantly inhibited the decrease of 5-HT in the hippocampus. These observations suggest that the effect of this drug on delayed neuronal death in the CA1 neurons in the hippocampus in Mongolian gerbils with occluded common carotid arteries may be related to the serotonergic system.

Minaprine, 3-(2-morpholinoethylamino)-4-methyl-6-phenyl pyridazine dihydrochloride, is a newly developed psychotropic drug effective for treating various types of depression seen clinically (1-3). We found that minaprine also has a protective effect against a variety of experimental cerebral anoxias and models of ischemia (4, 5). When minaprine was given to Mongolian gerbils before cerebral ischemia, a significant improvement of memory deficit was evident. In addition, there was no decrease in the amplitude of hippocampal theta waves. Destruction and disappearance of the CA1 neurons induced by a 5-min cerebral ischemia in Mongolian gerbils was considerably diminished (5).

Various changes occur in the concentration of monoamines and their metabolites during and after experimental ischemia (6-8). It is considered that changes in neurotransmitters during ischemia or after re-circulation may contribute to neuronal degradation (9, 10). We found that 5 min of cerebral ischemia in Mongolian gerbils caused disturbances in monoaminergic neurons during and immediately after, but not several days after re-circulation (manuscript in preparation). Thus, changes in neurotransmitters in the acute period may be related to delayed development of morphologically obvious cell death following reversible ischemia.

Minaprine was found to be effective in most animal models of depression, presumably by acting on central serotonergic, dopaminergic and cholinergic neurotransmission systems (11, 12). The present experiment were done to observe the effects of minaprine on changes in monoamines contents in Mongolian gerbils with occluded common carotid arteries.

Materials and Methods

Animals: Male Mongolian gerbils supplied by Shin Nihon Dobutsu (Saitama, Japan) weighing 60–80 g were housed in an air-conditioned room at 22±1°C. Light was provided on a 12 hr light-dark cycle with lights off at 7:00 p.m. Food and water were supplied ad lib. All the animals had become thoroughly familiar with being handled. The
number of animals in each group was 3–8.

**Surgical procedures:** The gerbils were lightly anesthetized with ether and placed in the supine position. After the local infiltration of xylocaine, both common carotid arteries were exposed through a ventral midline incision and carefully separated from the adjacent vein and sympathetic nerves, as described (13). The arteries were then clamped with aneurysm clips. After 5 min, the clips were removed and the skin was sutured. Sham operated animals were treated in the same manner, except for no clamping.

**Monoamines and metabolites assay:** The Mongolian gerbils were killed by a microwave applicator (TMW 6402, Toshiba, Tokyo, Japan) immediately after the 5-min of ischemia or 5 min, 30 min, 2 hr and 24 hr after re-circulation. The brain was removed and dissected into the cortex, striatum and hippocampus. Sample preparation was performed as described by Magnusson et al. (14). Each tissue was weighed and frozen in liquid nitrogen and kept at -60°C until analysis. Each tissue was homogenized in a 10-fold volume of 0.1 M ice-cold perchloric acid containing 1 mM EDTA-Na, 10 μM sodium pyrosulfite and 3,4-dihydroxy benzylamine, as an internal standard (100 ng/ml). After centrifugation for 15 min at 15000 rpm at 4°C, the supernatant were passed through a 0.45 μm millipore filter. The elute, 10–20 μl, was injected onto a high performance liquid chromatograph coupled with an electrochemical detector (HPLC-ECD). The HPLC-ECD system included an ODS-A column, a high-performance liquid chromatograph (YANAKO L-4000W, Yanagimoto, Co., Ltd.) and voltammetric detector (YANAKO VMD-501, Yanagimoto, Co., Ltd.). The mobile phase contained an 85:15 (v/v) mixture of 0.1 M citric acid-sodium acetate buffer (pH 3.7) and methanol containing octane sulfonic acid-Na (125 mg/l) and EDTA-Na (10 mg/l), according to Warunhoff (15).

**Drugs:** Minaprine (Sanofi) dissolved in saline in a dose of 50 mg/kg was given p.o. for 3 days by intubation, and cerebral ischemia was carried out 30 min after the last administration. The dose of minaprine is expressed in terms of the salt.

**Statistical analysis:** The results were analyzed using Student's t-test.

**Results**

**Effect of minaprine on the contents of monoamines and their metabolites in naive Mongolian gerbils:** Tables 1–3 show the effect of minaprine on the levels of monoamines and their metabolites in the cortex, hippocampus and striatum. The contents of homovanillic acid (HVA) in the cortex and 3,4-dihydroxyphenyl acetic acid (DOPAC) in the striatum were significantly increased and decreased at 30 min after the administration of minaprine, respectively (Tables 1 and 3). 3-Methoxytyramine (3-MT) in the striatum increased significantly at 30 min after the administration of minaprine (Table 3).

**Effect of minaprine on changes in monoamine contents in Mongolian gerbils with 5-min common carotid arteries occlusion:** Noradrenaline (NA), dopamine (DA) and serotonin (5-HT) remained unchanged during 5-min of occlusion (Tables 1, 2 and 3). Minaprine slightly decreased the content of NA in the cortex and striatum during 5-min occlusion. NA levels in the cortex at 30 min and 2 hr, in the hippocampus at 5 min–2 hr, and in the striatum at 2 hr after re-circulation significantly decreased. Minaprine slightly ameliorated the decrease of NA in the hippocampus at 5 min after re-circulation. 5-HT levels in the hippocampus and striatum decreased significantly at 5–30 min and 30 min after re-circulation, respectively. Minaprine significantly ameliorated the decrease of 5-HT content in the hippocampus at 5–30 min after re-circulation (Fig. 1). DA levels were not changed after re-circulation.

**Effect of minaprine on changes in metabolites of monoamines in Mongolian gerbils with a 5-min occlusion of the common carotid arteries:** 5-Hydroxyindol acetic acid (5-HIAA), HVA and DOPAC levels remained unchanged during the ischemia (Tables 1, 2 and 3). 5-HIAA significantly increased in the striatum 30 min–2 hr after re-circulation, and minaprine significantly ameliorated this effect 30 min after re-circulation (Fig. 1). The levels of DOPAC in the striatum were increased at 5–30 min after re-circulation (Table 3). The levels of DOPAC in the striatum were increased at 5–30 min after re-circulation, and minaprine significantly ameliorated the increase of DOPAC at 5–30 min after reflow.
|                  | NA (μg/g)  | DA (μg/g)  | HVA (μg/g)  | 5-HT (μg/g) | 5-HIAA (μg/g) |
|------------------|------------|------------|-------------|-------------|---------------|
| **Non-ischemic group** |            |            |             |             |               |
| Saline           | 0.448±0.015| 0.161±0.022| 0.025±0.004 | 0.842±0.045 | 0.107±0.005   |
| Minaprine        | 0.414±0.031| 0.240±0.030| 0.048±0.007*| 1.203±0.145 | 0.129±0.008   |
| **After re-circulation** |            |            |             |             |               |
| 0 min            |            |            |             |             |               |
| Saline           | 0.356±0.016| 0.158±0.012| 0.059±0.009 | 0.832±0.055 | 0.214±0.039   |
| Minaprine        | 0.307±0.012*| 0.178±0.019| 0.034±0.002*| 0.802±0.024 | 0.111±0.051*  |
| 5 min            |            |            |             |             |               |
| Saline           | 0.242±0.007| 0.185±0.017| 0.072±0.004 | 0.567±0.033 | 0.194±0.030   |
| Minaprine        | 0.367±0.034*| 0.184±0.020| 0.061±0.005 | 1.041±0.114*| 0.178±0.018   |
| 30 min           |            |            |             |             |               |
| Saline           | 0.209±0.006**| 0.217±0.022| 0.108±0.010**| 0.712±0.022 | 0.199±0.010*  |
| Minaprine        | 0.215±0.014| 0.319±0.040| 0.106±0.012 | 0.801±0.038 | 0.162±0.010*  |
| 2 hr             |            |            |             |             |               |
| Saline           | 0.261±0.024*| 0.199±0.024| 0.094±0.007**| 0.829±0.035 | 0.184±0.006   |
| Minaprine        | 0.253±0.015| 0.244±0.028| 0.113±0.006 | 0.836±0.058 | 0.215±0.019   |
| 24 hr            |            |            |             |             |               |
| Saline           | 0.378±0.012| 0.267±0.023| 0.056±0.005 | 0.761±0.021 | 0.152±0.007   |
| Minaprine        | 0.433±0.012**| 0.207±0.021| 0.045±0.002 | 0.912±0.025 | 0.160±0.011   |

*P<0.05, **P<0.01, significantly different from the non-ischemic animals. *P<0.05, **P<0.01, significantly different from the minaprine and saline administered animals. Each value represents means±S.E.M.
Table 2. Effect of minaprine on changes in monoamine contents in the hippocampus in Mongolian gerbils with 5-min occlusion of common carotid arteries

|                  | NA     | DA     | HVA  | 5-HT   | 5-HIAA |
|------------------|--------|--------|------|--------|--------|
|                  | μg/g   | μg/g   | μg/g | μg/g   | μg/g   |
| **Non-ischemic group** |        |        |      |        |        |
| saline           | 0.475±0.039 | 0.104±0.014 | 0.032±0.004 | 1.396±0.040 | 0.266±0.031 |
| minaprine        | 0.394±0.020 | 0.146±0.021 | 0.038±0.002 | 1.487±0.127 | 0.237±0.014 |
| **After re-circulation** |        |        |      |        |        |
| 0 min            |        |        |      |        |        |
| saline           | 0.402±0.021 | 0.098±0.005 | 0.032±0.002 | 1.208±0.053 | 0.226±0.014 |
| minaprine        | 0.347±0.018 | 0.076±0.006* | 0.037±0.005 | 1.319±0.056 | 0.213±0.011 |
| 5 min            |        |        |      |        |        |
| saline           | 0.278±0.013** | 0.137±0.038 | 0.056±0.007 | 0.781±0.045** | 0.337±0.053 |
| minaprine        | 0.379±0.026* | 0.115±0.017 | 0.048±0.009 | 1.399±0.187* | 0.336±0.015 |
| 30 min           |        |        |      |        |        |
| saline           | 0.201±0.014** | 0.137±0.012 | 0.079±0.005 | 0.831±0.044** | 0.366±0.031 |
| minaprine        | 0.251±0.021 | 0.203±0.013** | 0.080±0.004 | 1.184±0.093** | 0.315±0.023 |
| 2 hr             |        |        |      |        |        |
| saline           | 0.242±0.018** | 0.131±0.016 | 0.099±0.009** | 1.148±0.036 | 0.360±0.016 |
| minaprine        | 0.204±0.016 | 0.147±0.014 | 0.091±0.006 | 1.033±0.045 | 0.377±0.037 |
| 24 hr            |        |        |      |        |        |
| saline           | 0.368±0.011 | 0.100±0.004 | 0.034±0.004 | 1.007±0.046** | 0.233±0.010 |
| minaprine        | 0.429±0.017 | 0.098±0.006 | 0.033±0.004 | 1.197±0.034** | 0.276±0.015* |

**P<0.01, significantly different from the non-ischemic animals. *P<0.05, **P<0.01, significantly different from the minaprine and saline administered animals. Each value represents means±S.E.M.
Table 3. Effect of minaprine on changes in monoamine contents in the striatum in Mongolian gerbils with 5-min occlusion of common carotid arteries

|                | NA (μg/g) | DA (μg/g) | DOPAC (μg/g) | HVA (μg/g) | 3-MT (μg/g) | 5-HT (μg/g) | 5-HIAA (μg/g) |
|----------------|-----------|-----------|--------------|------------|-------------|-------------|---------------|
| **Non-ischemic group** |           |           |              |            |             |             |               |
| saline         | 0.595±0.019 | 19.644±1.156 | 0.521±0.049 | 1.172±0.127 | 0.118±0.014 | 1.623±0.071 | 0.325±0.019   |
| minaprine      | 0.592±0.031 | 22.031±1.194 | 0.356±0.019* | 1.134±0.047 | 0.489±0.032*** | 1.940±0.129 | 0.363±0.021   |
| **After re-circulation** |       |           |              |            |             |             |               |
| 0 min          |           |           |              |            |             |             |               |
| saline         | 0.631±0.024 | 17.765±0.706 | 0.553±0.028 | 1.245±0.081 | 1.558±0.093* | 1.770±0.080 | 0.349±0.021   |
| minaprine      | 0.535±0.028* | 15.718±1.392 | 0.265±0.028*** | 0.976±0.076* | 1.714±0.116 | 1.766±0.117 | 0.307±0.020   |
| 5 min          |           |           |              |            |             |             |               |
| saline         | 0.555±0.052 | 12.426±0.921 | 1.806±0.133 | 1.374±0.121 | 1.201±0.114 | 1.167±0.103 | 0.565±0.060   |
| minaprine      | 0.597±0.066 | 17.644±1.755 | 1.004±0.181* | 1.262±0.045 | 2.560±0.326* | 1.761±0.149* | 0.508±0.033   |
| 30 min         |           |           |              |            |             |             |               |
| saline         | 0.467±0.014 | 18.950±1.376 | 1.249±0.103 | 2.736±0.181** | 0.174±0.023 | 1.193±0.050** | 0.641±0.032** |
| minaprine      | 0.388±0.022* | 16.864±1.064 | 0.595±0.040*** | 1.880±0.110** | 0.861±0.101*** | 1.220±0.061 || 0.444±0.021*** |
| 2 hr           |           |           |              |            |             |             |               |
| saline         | 0.436±0.016** | 15.536±0.732 | 0.550±0.038 | 2.300±0.133** | 0.139±0.022 | 1.324±0.047 | 0.575±0.030** |
| minaprine      | 0.477±0.019 | 15.645±0.660 | 0.467±0.035 | 2.092±0.062 | 0.277±0.034** | 1.438±0.060 | 0.584±0.042   |
| 24 hr          |           |           |              |            |             |             |               |
| saline         | 0.526±0.026 | 15.306±0.753 | 0.445±0.038 | 1.142±0.116 | 0.101±0.024 | 1.330±0.047 | 0.353±0.031   |
| minaprine      | 0.507±0.012 | 17.278±0.408* | 0.448±0.027 | 1.309±0.052 | 0.162±0.021 | 1.471±0.039* | 0.360±0.015   |

*P<0.05, **P<0.01, significantly different from the non-ischemic animals.  *P<0.05, **P<0.01, ***P<0.001, significantly different from the minaprine and saline administered animals. Each value represents means±S.E.M.
Fig. 1. Effect of minaprine on changes in serotonin content in the hippocampus in Mongolian gerbils with 5-min common carotid arteries occlusion. ***P<0.01, significantly different from the non-ischemic animals. *P<0.05, **P<0.01, significantly different from findings in minaprine and saline administered animals. O—O saline administered group, •—• minaprine administered group.

Fig. 2. Effect of minaprine on 3,4-dihydroxyphenyl acetic acid content in the striatum in Mongolian gerbils with 5-min occlusion of the common carotid arteries. *P<0.05, ***P<0.001, significantly different from the minaprine and saline administered animals. O—O saline administered group, •—• minaprine administered group.

(Fig. 2). 3-MT level in the atriatum increased markedly during ischemia (Table 3). Minaprine facilitated the increase of 3-MT at 5 min—2 hr after re-circulation.

Discussion
Neurons in the hippocampal CA1 subfield showed a delayed death, that is, destruction
of the CA1 neurons appeared from 2 or 3 days after the ischemic insult, and disappeared for the most part by day 7 (13, 16–18). It was reported that various changes occurred in monoamine concentrations during and after experimental ischemia (6–8). We found that although there were no changes in monoamines and their metabolites except for 5-MT during 5 min ischemia, the levels decreased or increased significantly immediately after re-circulation. However, at 3 and 7 days after re-circulation, there were no changes in the contents of monoamines and their metabolites (manuscript in preparation). If monoamines and their metabolites do relate to neuronal degradation, changes at 5 min to several hr after re-circulation may play an important role. Koide et al. (19) suggested that catecholamines ameliorate ischemic brain damage, as deduced by findings when a mixture of adrenaline and noradrenaline was infused during the early re-circulation period in animals with an induced ischemia, including bilateral carotid arteries clamping and reduction of blood pressure to 40–50 mmHg by bleeding and administration of trimethaphan. Blomquist et al. (20) reported that bilateral lesion of the locus coeruleus aggravated the neuronal necrosis in the CA1 region and neocortex following complete cerebral ischemia induced by transient cardiac arrest. Namely, the post-ischemic activation of the inhibitory locus coeruleus system could counteract a possible detrimental neuronal hyperexcitation. Welch et al. (21) reported that the incidence of ischemia induced by unilateral common carotid artery occlusion decreased from 44% to 26% in p-chlorophenylalanine-treated animals.

We reported that when minaprine was administered in a dose of 50 mg/kg at 30 min before occlusion, Nissl's degradation and destruction and disappearance of the CA1 neurons were significantly ameliorated (5). In the present experiment, minaprine inhibited significantly the decrease of NA only at 5 min after re-circulation in the hippocampus. Minaprine also inhibited markedly the decrease of 5-HT at 5 and 30 min after re-circulation. Therefore, the mechanisms of action of minaprine in the inhibition of delayed neuronal death in CA1 neurons in the hippocampus induced by 5-min occlusion of bilateral carotid arteries may be related to the serotonergic system.

Biochemical studies in rats have shown that minaprine raises 5-HT concentrations in the striatum, hypothalamus, parietal cortex and brain stem (12). In the present study on Mongolian gerbils, minaprine slightly increased 5-HT contents in naïve animals. Part of this effect could be related to the inhibition of type A MAO by minaprine (22). Indeed, 5-HT in the brain are selectively deaminated by type A MAO (23). Kan et al. reported that minaprine behaves as a moderate and short acting MAO A inhibitor and is devoid of any significant activity on 5-HT uptake or release in naïve rats (22). The effect of minaprine on delayed neuronal death in Mongolian gerbils with occluded common carotid arteries may relate to the inhibition of abnormalities of 5-HT transmission. Further investigations are warranted because events related to the minaprine normalization of 5-HT levels in the hippocampus at 5 min–24 hr after re-circulation were not clarified.

In the striatum, we found that minaprine raised 3-MT levels and decreased those of DOPAC in the striatum, as it did in rats (22). In the ischemic model, DOPAC and HVA levels increased at 5–30 min and at 30 min–2 hr after re-circulation, respectively, and minaprine ameliorated these changes. The increase of 3-MT induced by ischemia was significantly potentiated by minaprine. The effect of minaprine on the dopaminergic system in the striatum in naïve animals may explain these phenomena.

According to mechanisms related to delayed neuronal death, intracellular calcium overload (24), the release of excitotoxin (25), accumulation of free fatty acid (26), alterations of protein synthesis (27) and so on may be involved. The delayed neuronal death inhibition seen with minaprine remains the subject of ongoing studies.

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