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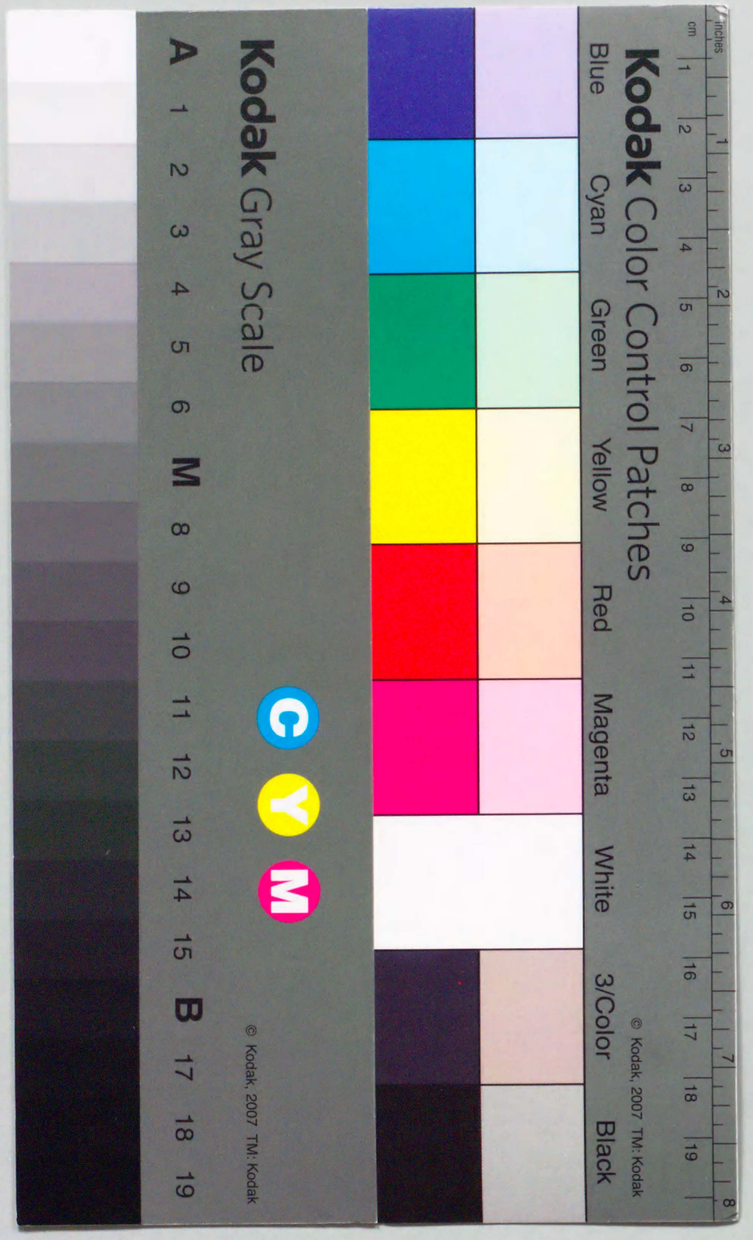

Plasma-Free and Sulfoconjugated MHPG in Major Depressive Disorders: Differences between Responders to Treatment and Nonresponders

Kazunori Mine, Mitsuko Okada, Norio Mishima, Michihiro Fujiwara, and Tetsuya Nakagawa

The plasma levels of free and sulfoconjugated forms of 3-methoxy-4-hydroxyphenylglycol (MHPG) were examined before and after treatment in 16 patients with unipolar major depressive disorders without melancholia. The patients were treated with intravenous administration of clomipramine for 4 weeks. Seven depressive disorder patients who showed marked improvement (the improvement group) revealed significant reduction in their plasma sulfoconjugated MHPG levels. In 6 depressive disorder patients who showed no improvement (the no-improvement group), the plasma sulfoconjugated MHPG levels showed no significant change after treatment. The remaining 3 patients, who showed ambiguous change after treatment, were excluded from the analysis. Levels of plasma-free MHPG showed significant change after treatment in neither the improvement group nor in the no-improvement group. It is suggested that levels of plasma sulfoconjugated MHPG may serve as an indicator of brain noradrenergic activity.

Key Words: Plasma, sulfoconjugated MHPG, major depressive disorder, antidepressant, clomipramine infusion, blood–brain barrier

Introduction

It has been suggested that a dysregulation of the brain noradrenergic system (NE system) may be a causative factor in affective disorders (see Siever 1987). However, in spite of many previous studies, a useful clinical index that shows how noradrenergic activity (NE activity) in the central nervous system (CNS) is reflected in peripheral body fluids has not yet been established.

Because 3-methoxy-4-hydroxyphenylglycol (MHPG) is considered to be the main metabolite of norepinephrine (NE) in the brain (Axelrod et al 1959; Schanberg et al 1968), MHPG output in urine (Linnoila et al 1982), MHPG levels in cerebrospinal fluid (CSF) (Peabody et al 1987), and free MHPG levels in plasma have been measured as possible indices of brain NE activity in humans (Charney et al 1981a; Siever and Uhde 1984; Roy et al 1986; Siever et al 1986; Mazure et al 1987; Pohl et al 1987; Bowers et al 1988).

In attempts to establish the relationship between the brain NE system and affective disorders, the free MHPG

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levels in CSF have been examined as the most feasible reflection of brain NE activity (see Siever 1987). Since a high correlation has been observed between free MHPG levels in plasma and free MHPG levels in CSF in humans (Kopin et al 1983), the relationship between free MHPG levels in plasma and affective disorders has been investigated (Charney et al 1981a; Siever and Uhde 1984; Roy et al 1986; Siever et al 1986; Mazure et al 1987; Pohl et al 1987; Bowers et al 1988; Pliszka et al 1988). However, it seems that no relationship between free MHPG levels in plasma and depressive disorders has been documented. Several investigators have suggested that in humans, the MHPG levels in lumbar CSF must be considered to be an uncertain indicator of NE metabolism in the CNS. Kessler et al (1976) indicated that in rhesus monkeys lumbar CSF levels of MHPG in large part reflect spinal cord NE metabolism, rather than brain NE metabolism. Moreover, Degrell and Nagy (1990) reported that there is no significant correlation between levels of MHPG in the cisternal CSF and plasma levels of MHPG in humans. On the other hand, recent reports have suggested that free MHPG in plasma is derived largely from plasma NE, reflecting peripheral sympathetic activity (Kopin 1984, Roy et al 1986; Pohl et al 1987; Sevy et al 1989).

It has been shown that sulfoconjugated MHPG and phenol sulfotransferase (PST), which catabolizes the sulfoconjugation of phenol, exist in the human CNS (Karoum et al 1977; Young et al 1984), and it has been suggested that sulfoconjugation may play an important role in the metabolism of NE (Axelrod et al 1959). Although it has been considered that the sulfoconjugation of MHPG may be involved in its removal from the brain (Foldes and Meek 1974; Takahashi et al 1977), only a few preliminary studies have been reported concerning the relationship between plasma sulfoconjugated MHPG levels and depressive disorders (Sweeney et al 1980; Jimerson et al 1981). For example, Sweeney et al (1980) showed a significant test–retest reliability in levels of both plasma free- and sulfoconjugated MHPG, but they found no significant correlation between plasma-free and sulfoconjugated MHPG. Jimerson et al (1981) showed that the total levels of plasma MHPG were significantly higher in excited states than in depressive states for both a patient with bipolar affective disorder and for a patient with schizoaffective disorder.

Recently, it has been found that PST exists in the bovine brain microvessel endothelium and it has also been suggested that sulfoconjugation may play a role in regulating catecholamine movement at the blood–brain barrier (BBB) (Baranczyk-Kuzma et al 1986). It has been speculated that PST also may play a role in the termination of the neurotransmitter actions of catecholamines (Young et al 1984).

In a preliminary study by the author, the plasma levels of free and sulfoconjugated forms of MHPG were examined before and after treatment in patients with unipolar major depressive disorders without melancholia. All patients were treated with various antidepressants via various routes. In 11 patients showing a good response to treatment, the plasma-sulfoconjugated MHPG levels were significantly reduced, whereas no significant changes were seen in 9 patients showing no response to treatment. In a comparison group of 6 patients with somatic diseases, the plasma-sulfoconjugated MHPG levels showed a strong tendency to increase after treatment. Based on the results of this preliminary study, we assume that plasma-conjugated MHPG may reflect the activity of the NE system in the CNS.

This study was undertaken in order to investigate the potential relationship between plasma MHPG levels and major depressive disorders. Because depressive disorders may consist of etiologically heterogeneous subgroups, only patients with a unipolar major depressive disorder with no current or past history of melancholia were studied. To further explore relationships revealed in our preliminary study, refinements in treatment techniques were made and the measures of plasma-free and conjugated MHPG levels were repeated for a fixed period with the patients.

Subjects and Methods

Sixteen patients who fulfilled the DSM-III-R criteria for major depressive disorders with no current or past history of melancholia who were admitted to the Department of Psychosomatic Medicine at Kyushu University in Fukuoka, Japan, participated in this study. All of the patients had been admitted because of impairment in their normal life and work. None of the patients with major depressive disorders had been previously treated for depressive disorders and they all had been free of tricyclic and tetracyclic antidepressant medications and sulpiride medication prior to this study. Some of the patients previously had been given small doses of benzodiazepines, but these patients were kept medication free for at least one week before the study began. All subjects gave their written informed consent prior to participation in this study.

All patients were treated with intravenous administration of clomipramine only. The patients received a clomipramine infusion every afternoon for 28 days. The beginning doses and the maximum doses were determined according to the patients' body weights and their complaints of unpleasant side effects, such as nausea and vomiting. Each patient was asked to fast from midnight to 8:00 AM. The patient then was asked to lie flat on a bed for 30 min, after which a 10-ml sample of heparinized blood was obtained by venipuncture.

Initial blood samples were obtained on the morning of the day when clomipramine infusion started and additional

blood samples were collected on the 7th, 14th, 21st, and 28th days after the start of treatment. On the same days as the blood samples were obtained, ratings on the Hamilton Depression Rating Scale (HDRS) were determined. Patients were designated as belonging to the "improvement" group if they showed a 60% or greater decrease in their HDRS scores by the end of the 28-day treatment period. Patients who showed less than a 20% decrease in HDRS scores were placed in the "no-improvement" group. Patients whose HDRS scores showed a decrease of 21% to 59% were regarded as ambiguous cases and were omitted from the remainder of the analysis.

Blood samples for plasma NE and MHPG were centrifuged for 20 min within one-half hour following collection. Plasma aliquots were separated from these samples and stored at −40°C.

Plasma-free and sulfoconjugated MHPG levels were measured in duplicate by a method developed by the authors (Okada et al 1988). Plasma-free MHPG levels were determined using HPLC-ECD after deproteinization by concentrated perchloric acid and extraction with SEP PAK cartridges. The plasma total MHPG levels were measured simultaneously using the same method as was used to measure free levels after enzymatic hydrolysis with 50 units of sulfatase type H-5 for 18 hours. The levels of sulfoconjugated MHPG in each sample were defined as the differences between the total and free levels.

Repeated measures analysis of variance was used to look for significant differences between the improvement group and the no-improvement group in change in levels of free and sulfoconjugated MHPG. Significance levels were determined based on the Greehouse and Geisser adjustment (1959). The GLM procedure of SAS was utilized.

Results

Seven patients were categorized as belonging to the improvement group, while six patients were placed in the no-improvement group. The remaining three patients were regarded as ambiguous cases and were excluded from the analysis. The range of the decrease in HDRS scores of the ambiguous cases was from 32 to 48%. The mean number of doses of clomipramine infused was 28.7 ± 13.5 (SD) mg/day for the improvement group and 34.6 ± 9.9 (SD) mg/day for the no-improvement group.

When the improvement and no-improvement groups were compared in terms of overall change in plasma sulfoconjugated MHPG levels, a markedly significant difference was found ($F = 5.75$; df = 4, 44; $p < 0.01$). The plasma-sulfoconjugated MHPG level of the improvement group decreased significantly, whereas the level for the no-improvement group remained relatively constant over the 28-day treatment period. Furthermore, the level of plasma-sulfoconjugated MHPG in the improvement group declined significantly from the initial level at each measurement period during treatment. At the end of one week of treatment, the level had dropped significantly from the initial level ($F = 10.11$; df = 1, 6; $p < 0.02$). Each succeeding week of treatment witnessed an increasingly significant decline: after two weeks, $F = 13.71$; df = 1, 6; $p < 0.02$; after three weeks, $F = 26.27$; df = 1, 6; $p < 0.01$; after four weeks, $F = 52.57$; df = 1, 6; $p < 0.001$. On the other hand, plasma-free levels of MHPG showed no significant change during the treatment period for either the improvement or the no-improvement group.

The clinical course and the changes in plasma-free and sulfoconjugated MHPG levels of each patient in the improvement group are shown in Figure 1. The same information for patients in the no-improvement group is presented in Figure 2.

Discussion

In this study, the drug, the method of administration, and the treatment period were all standardized. All patients received an intravenous infusion of clomipramine every day for four weeks.

Patients who showed marked improvement (the improvement group) revealed significant reductions in levels of plasma-sulfoconjugated MHPG but no change in levels of free MHPG. Patients who showed little improvement (the no-improvement group) showed no significant change in levels of either plasma-free or sulfoconjugated MHPG. It is suggested that a significant decrease in plasma-sulfoconjugated MHPG level may be specifically related to the successful outcome of the treatment of major depressive disorder and it can be speculated that plasma-sulfoconjugated MHPG might reflect NE activity in the CNS.

It is interesting that levels of plasma-free MHPG showed no significant change after treatment in either of the groups. Charney et al (1981a) reported that the administration of desipramine induced a significant reduction in plasma free MHPG in patients with major depressive disorder with melancholy, and that the effect was not related to patients' response to treatment. Moreover, a similar effect of desipramine on plasma-free MHPG in normal humans was suggested by Zavadil et al (1984). It is difficult to explain why our results differ from theirs. However, it can be pointed out that, in our study, major depressive disorders without melancholy were investigated and that their studies were made on different subgroups of depressive disorders or on normal volunteers.

Extein et al (1973) demonstrated the significant accumulation of sulfoconjugated MHPG in the brain following probenecid treatment in rabbits and suggested that sulfoconjugated MHPG is transported out of the CNS by a

IMPROVEMENT GROUP

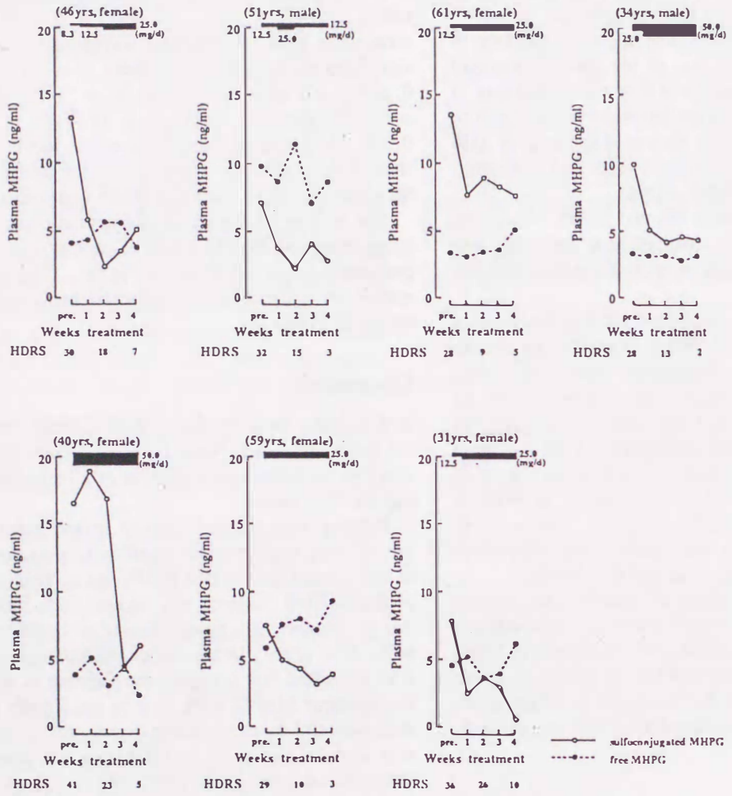

Figure 1. Effect of intravenous infusion of clomipramine on plasma-free MHPG levels (closed circle) and sulfoconjugated MHPG (open circle) in the improvement group.

probenecid-sensitive mechanism. Meek and Neff (1972) found that in rats 3-methoxy-4-hydroxy-mandelic acid (VMA) and sulfoconjugated MHPG, but not free MHPG, are eliminated from the brain by a probenecid-sensitive transport system that is similar to the system that rids the brain of both homovanilic acid (HVA), and 5-hydoxyindoleacetic acid (HIAA). They suggested that MHPG is converted to sulfoconjugated MHPG and then transported from the brain. It was proposed that MHPG, which is produced in the brain and is a nonpolar compound, may be secreted from CSF into plasma by passive diffusion and bulk flow (Kopin et al 1983). This mechanism for secreting MHPG from CSF into plasma may exist in humans. However, a faster transport mechanism for regulating the elimination of MHPG from the CNS to the blood appears to be necessary in order to maintain homeostasis in the human brain with its highly developed NE system. It thus can be speculated that most MHPG, which is pH neutral, may be converted to sulfoconjugated MHPG of an acidic nature and then eliminated from the CNS into the circulation by an active transport mechanism through the BBB. Karoum et al (1977) showed that a sizable proportion of sulfoconjugated MHPG exists in the human brain. Young et al (1984) showed that the human brain contains two forms of PST: a thermostable form that catalyzes the sulfoconjugation of phenols and a thermolabile

NO-IMPROVEMENT GROUP

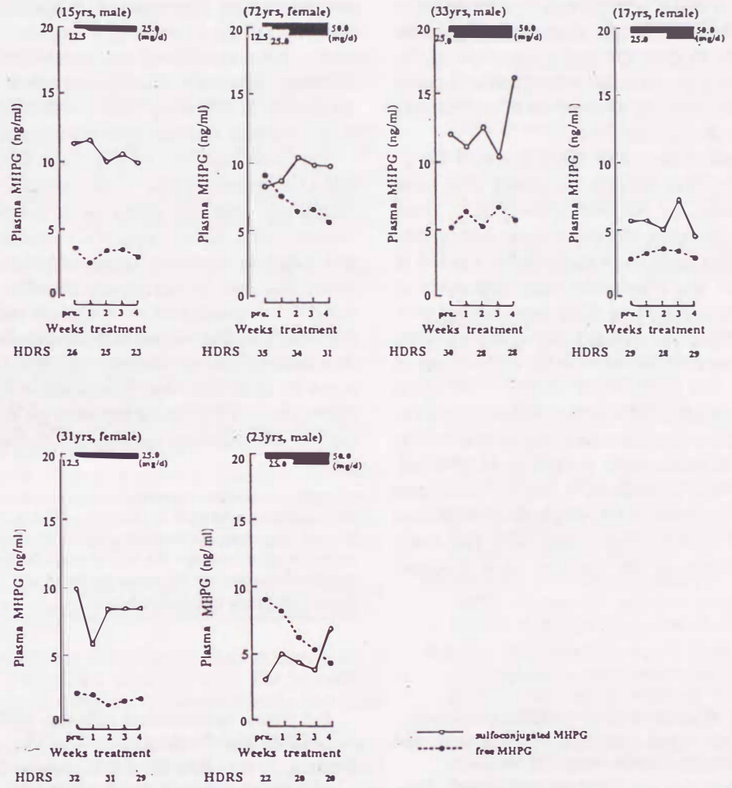

Figure 2. Effect of intravenous infusion of clomipramine on plasma-free MHPG levels (closed circle) and sulfoconjugated MHPG (open circle) in the no-improvement group.

form that catalyzes the sulfoconjugation of catecholamines. In addition, they found that both forms of PST activities are highest in the cerebral cortex. Baranczyk-Kuzma et al (1986) demonstrated significant PST activity in bovine microvessel endothelial cell monolayers. They also indicated that PST may play a role in regulating the movement of phenolic substances across the BBB and that the PST is of a thermostable form. Baranczyk-Kuzma et al (1989) investigated the substrate specificity of thermostable PST from a primary culture of bovine brain microvessel endothelial cell monolayers and found that thermostable PST from bovine brain microvessel endothelium does not utilize endogenous catecholamines as substrates. MHPG and VMA, however, exhibited high activity as substrates, compared to p-nitrophenol as the substrate for the PST. The substrate specificity of PST associated with brain microvessel endothelial cells suggests a role for the sulfation at the BBB in regulating the direct movement of NE metabolites between the blood and the brain.

Spector (1989) hypothesized that the route through the choroid plexus, which acts as a barrier between the blood and the CSF while pumping materials from the blood into the CSF and cleaning the CSF of waste substances that form in the brain tissue, may have been more important

for transporting major substances at earlier stages of mammalian evolution, when the forebrain was still relatively small and the choroid plexus was proportionally large. With the great evolutionary expansion of the forebrain in human beings, the larger networks of cerebral capillaries might be better able to meet the major demands of the mammalian brain. It is possible that this hypothesis could be applicable to the metabolic derivatives of neurotransmitters produced in the human brain.

Our results regarding depressive disorders with favorable therapeutic outcomes are thus consistent with most of the inferences made by previous investigators. Such investigators have concluded that the chronic administration of antidepressants leads to an increased efficiency in the brain NE system and reduces the rate of turnover of brain NE in depressive disorders. They have further concluded that the antidepressant efficacy may involve a direct or indirect inhibition of NE turnover in the CNS (Maas et al 1972; Svensson and Usdin 1978; Sulser et al 1978; Charney et al 1981b; Linnoila et al 1982). Although plasma-sulfoconjugated MHPG concentrations may be affected by either peripheral NE metabolism, peripheral MHPG sulfoconjugation, or renal clearances, it can be postulated that plasma-sulfoconjugated MHPG might be an important index of brain NE activity. The results from our study might provide evidence of the presence of a transport mechanism that regulates the transendothelial passage of the NE metabolite, MHPG.

A special characteristic of this study is that the subjects, who had major depressive disorder without melancholy and who had no experience of treatment with antidepressants, were considered as a relatively homogeneous subgroup. However, this fact also gives rise to one of the limitations of this study, which is that the results may not be generalized to other types of depressive disorder.

The most important finding of this study is that plasma-sulfoconjugated MHPG levels changed according to the therapeutic outcome following intravenous infusion of clomipramine. Clomipramine is considered to be a potent and selective serotonin uptake inhibitor (Carlsson et al 1969). Recently, it was also reported that after intravenous infusion of clomipramine, the main metabolite, desmethylclomipramine—a potent NE uptake inhibitor—was not detectable in plasma (Golden et al 1989; Jarrett et al 1991). It can be speculated that clomipramine may affect the NE system in the CNS via the serotonergic system in the CNS. Further investigations are required to elucidate this mechanism.

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