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Enhanced norepinephrine output during longterm desipramine treatment: a possible role for the extraneuronal monoamine transporter (SLC22A3)

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Abstract

To study the delay (2–6 weeks) between initial administration of norepinephrine reuptake inhibitor antidepressants and onset of clinical antidepressant action, we examined the effects of desipramine treatment on urinary and plasma catecholamines and their metabolites during the initial 6 weeks of treatment in depressed patients. Catecholamines and metabolites in 24-hour urine collections and 8:00 a.m. plasma samples were measured at baseline and after 1, 4, and 6 weeks of desipramine treatment. Desipramine treatment produced significant increases in urinary norepinephrine (NE) and normetanephrine (NMN) and plasma NE at Weeks 4 and 6, but not at Week 1. The ratio of urinary NE/NMN was increased at Weeks 4 and 6, suggesting a reduction in the metabolism of NE to NMN at extraneuronal sites by Weeks 4 and 6. The increases in urinary NE and NMN and plasma NE at Weeks 4 and 6 of desipramine treatment were associated with a reduction in the conversion of NE to NMN. This would be compatible with a blockade of the extraneuronal monoamine transporter (organic cation transporter 3; SLC22A3) by NMN. Inhibition of the extraneuronal monoamine transporter may be an important component in the clinical pharmacology of the norepinephrine reuptake inhibitor antidepressant drugs, such as desipramine. The ClinicalTrials.gov Identifier for this study is NCT00320632.

Keywords

Extraneuronal monoamine transporter; SLC22A3; Norepinephrine; Desipramine; Depression

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1. Introduction

Tricyclic antidepressant drugs such as imipramine and desipramine as well as all other classes of antidepressants, including monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs), rapidly show pharmacological effects (e.g., effects on norepinephrine physiology and metabolism) after acute or short-term (1–2 days) drug administration. This time delay between the acute or short-term neuropharmacological effects of these antidepressants and their clinical antidepressant effects has posed a major problem in neuropsychopharmacology since the early 1960s (Katz et al., 2004).

Norepinephrine (NE) has been hypothesized to be functionally deficient in some depressed patients, and NE is thought to play an important role in the mechanisms of action of at least some antidepressant treatments, most notably, tricyclic antidepressants (Schildkraut, 1965; Ordway et al., 2003; Meyer et al., 2006). Measures of norepinephrine and its metabolites have also been reported to improve prediction of treatment response and diagnosis in patients with depressive illnesses (Schatzberg et al., 1980; 1981; 1989). To help understand why it may take up to 6 weeks for antidepressant drugs to exert their clinical antidepressant effects, we examined NE metabolism in depressed patients across 1, 4, and 6 weeks of treatment with the tricyclic antidepressant, desipramine, on NE metabolism in depressed patients. In this study, we simultaneously followed changes in both urinary catecholamines and metabolites and measures of plasma NE and 3-methoxy-4-hydroxyphenylglycol (MHPG) at multiple time points after the initiation of desipramine treatment.

2. Material and methods

The study protocol was approved by the Institutional Review Boards of McLean Hospital (Belmont, MA) and Massachusetts Mental Health Center and Harvard Medical School (Boston, MA). All subjects were recruited from newspaper advertisements or by referral from the clinical staff at McLean Hospital. On admission to the study, subjects were explained the nature and purpose of the study and gave their signed informed consent. The subjects were 15 (7 female and 8 male) depressed patients with mean age of 37.1 ± 12.8 (range 19–63) years. These subjects met full DSM-III-R criteria for unipolar major depressive disorder, based on a clinical interview using the Structured Clinical Interview for DSM-III-R (SCID) by a trained clinical research assistant who achieved acceptable inter-rater reliability (kappa >.7) with standard raters at the depression research facility at McLean Hospital. Untreated at intake, these depressed subjects scored a minimum of 19 on the Hamilton Depression Rating Scale (HDRS), 21-item version; and the mean baseline HDRS score (±1SD) was 23.7 ± 3.9 (range: 1–34). All subjects had been free of all psychoactive medication, aspirin, and nonsteroidal anti-inflammatory agents for a minimum of two weeks prior to study (6 months for serotonergic agents and monoamine oxidase inhibitors), showed no drug or alcohol abuse in the previous six months, and evidenced no major medical disorders.

Throughout the treatment phase (Weeks 1–6), the clinical response was assessed weekly using the HDRS. Blood samples and 24-hour urine collections were obtained at baseline, and at Weeks 1, 4, and 6 of treatment. Initially, patients were given 50 mg desipramine in the evening. This was increased to 100 mg per day by Day 4 and to 150 mg per day on Day 11. If a patient showed a HDRS decrease of 40% or more by Day 22, the dose of desipramine was not increased, but continued at 150 mg per day and maintained at that level provided the HDRS score continued to decrease. Alternatively, if the patient did not have at least a 40% decrease from the baseline HDRS score by Day 22, and there were no medical contraindications or manifestations of toxicity, the desipramine dosage was increased to 250mg per day, with a subsequent further increase, if HDRS scores had not decreased by 60% or more, to the maximum dosage of 300 mg per day by Day 30 (if clinically tolerated).

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2.1 Biochemical Methods

Urine and Plasma Collection Procedures—Subjects were given detailed instructions concerning the collection of three consecutive 24-hour urine collections prior to each visit, and the completeness of these collections was ascertained by careful interview at each visit. In addition, the consistency of 24-hour urine volumes and creatinine levels were used to assess the completeness of individual urine collections within each patient. The 24-hour urine collections were obtained using acetic acid as preservative according to long-established procedures in our laboratory, and multiple aliquots were stored frozen at −20° C in separate bottles until assayed. For each urine-based measure, the average (mean) of the three consecutive collections was used in the statistical data analyses. A blood specimen was obtained at the end of the time period during which the urine specimens were collected. Between 7:30 and 8:30 a.m. on the day on which urine collections were completed, approximately 20 ml of whole blood were collected from each subject into heparinized tubes, and plasma specimens were prepared using standard procedures in accordance with the requirements of each assay.

Urinary Catecholamines—NE and epinephrine (E) were determined by high performance liquid chromatography (HPLC) using an electrochemical detector following modification of the method of Wu & Gornet (1985). Interassay coefficients of variation: NE = 4.4%; E = 7.1%.

Urinary Normetanephrine (NMN) and Metanephrine (MN)—Urinary NMN and MN were determined by HPLC using an electrochemical detector following modifications of the method of Orsulak et al. (1983). Interassay coefficients of variation: NMN = 4.0%; MN = 4.0%.

Urinary 3-Methoxy-4-hydroxyphenylglycol (MHPG)—Urinary MHPG was determined by gas chromatography using an electron capture detector following the method of Dekirmenjian & Maas (1970). Interassay coefficient of variation was 8.1%.

Urinary Vanillylmandelic Acid (VMA)—Urinary VMA was determined by HPLC using an electrochemical detector following modifications of the method of Moleman & Borstrok (1983). Interassay coefficient of variation = 2.5%

Plasma NE, E, and Dopamine (DA)—NE, E, and DA were determined by HPLC with dihydroxybenzylamine as the internal standard using a modification of the method of Bouloux et al. (1985). Free NE, E, and DA were determined quantitatively using a dual electrode electrochemical detector. The interassay coefficients of variation were 7.0% for NE, 8.2% for E, and 16.8% for DA.

Plasma MHPG—Plasma MHPG was determined by HPLC with 3-ethoxy-4-hydroxyphenylglycol (EHPG) as the internal standard following a modification of the method of Hariharan et al. (1989). MHPG was determined quantitatively using a dual electrode electrochemical detector. The interassay coefficient of variation for MHPG was 4.6%.

Plasma Homovanillic Acid (HVA)—Plasma HVA was determined by HPLC with 5-fluoro-HVA as the internal standard following a modification of the method of Chang, et al. (1983). HVA was determined quantitatively using a dual electrode electrochemical detector. The interassay coefficient of variation for HVA was 5.2%.

Urinary Creatinine—Urinary creatinine was determined using the Beckman Creatinine II Analyzer by a modification of the Jaffe reaction. Interassay coefficient of variation was 2.0%.

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2.2 Statistical Methods

Visit-specific determinations of the above mentioned study variables were entered into a panel (subject-by-time) dataset. For all these variables, both change-from-baseline and percent-change-from-baseline measures were obtained at each post-baseline visit. Change-from-baseline data were summarized as means ± standard deviations (SD). Intent-to-treat methods were used. Change-over-time in the outcome measures was assessed using random effects regression modeling methods, permitting inclusion of repeated measures within subjects. Indicator (0/1) variables defined at Weeks 1, 4, and 6 enabled assessment-specific change-from-baseline contrasts and post-modeling pairwise contrasts among the 3 post-baseline assessments. Overall model strength of the random effects models was assessed via χ^2[df=3] statistics. Some continuous measures were logarithmically transformed to achieve distributions closer to Gaussian prior to modeling. Partial residual plots were checked to assess the adequacy of modeling fits. Statistical significance required 2-tailed $p<.05$. Statistical analyses were carried out with Stata® software (Stata Corporation, College Station, TX 77845).

3. Results

Catecholamines and their metabolites were measured in urine and plasma from depressed patients at baseline, and after one, four and six weeks of continuous treatment with desipramine.

The primary study measures obtained at these four time periods included assessments of the urinary catecholamines and metabolites (NE, E, NMN, MN, MHPG, and VMA), and measures of plasma NE and plasma MHPG. In addition, HDRS data were obtained at these intervals. For all four time periods, there were only 24 (4.4%) missing observations out of a total of 540 study measures (15 subjects × four visits × nine variables). Seven subjects had one or more of these nine variables missing at one visit; and one subject had eight of these variables (all but the HDRS) missing at one visit.

Urinary levels of the deaminated *O*-methylated metabolites of NE, MHPG and VMA, were significantly decreased during Week 1 of treatment, and these changes persisted through Weeks 4 and 6 of treatment (Table 1). Similarly, plasma levels of MHPG were significantly decreased during Week 1 of treatment and remained significantly decreased at Weeks 4 and 6 (Table 2). Thus, during desipramine treatment, there were parallel decreases in 8:00 a.m. plasma MHPG and 24-hour urinary levels of MHPG and VMA relative to baseline. Changes in plasma levels of the deaminated *O*-methylated metabolite of DA, HVA, were not observed during the study (baseline plasma HVA: 12.2 ± 5.5 ng per ml).

In contrast to MHPG and VMA, there was no change in urinary (and plasma) NE and its *O*-methylated metabolite NMN after one week of treatment. However, significant increases in both 24-hour urinary NE and NMN were observed after four and six weeks of desipramine treatment (Table 1). Plasma levels of NE were unchanged after one week of treatment with desipramine, but plasma levels of NE increased after Weeks 4 and 6 of desipramine treatment (Table 2), in parallel with the changes in 24-hour urinary NE levels (Table 1). We also observed increases in plasma DA levels at Weeks 4 and 6 of treatment (Table 2).

There was no change in 24-hour urinary E (baseline urinary E: 7.3 ± 3.4 mcg per 24 hr) or its *O*-methylated metabolite MN (baseline urinary MN: 104 ± 40 mcg per 24 hr) at any time during the study. Moreover, no change in 8:00 a.m. plasma E levels was observed during the course of the study (baseline plasma E: 0.037 ± 0.018 ng per ml).

When compared to baseline, the mean molar ratio of urinary NE/NMN was significantly higher at Weeks 4 and 6 of desipramine treatment, especially at Week 6. These data were as follows: Baseline: 0.177 ± 0.05; Week 1: 0.204 ± 0.12 ($z = 1.59$, $p = 0.112$); Week 4: 0.207 ± 0.08 (z

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= 2.61, p = 0.009); Week 6: 0.223 ± 0.08 (z = 3.07, p = 0.002); overall chi-square [df = 3] = 9.63, p = 0.022. The increases in the ratio of urinary NE/NMN may reflect a reduction in the extraneuronal conversion of NE to normetanephrine during Weeks 4 and 6 of desipramine treatment (see Discussion below).

4. Discussion

In the present research study, levels of urinary MHPG and VMA (the major deaminated catechol metabolites of NE) and plasma MHPG were significantly decreased by Week 1 of treatment with desipramine and these decreases in urinary VMA and MHPG and plasma MHPG persisted through Week 4 and Week 6 of treatment (Tables 1 and 2). These decreases in 'whole body turnover' of NE during antidepressant treatment are consistent with previous observations from our laboratory and other investigators (Schildkraut et al., 1964 and 1972;Linnoila et al., 1982;Golden et al., 1988).

The major mechanism for the removal of NE from the synaptic space is reuptake by the NE transporter (Uptake 1) in the presynaptic membrane (Eisenhofer, 2005). In preclinical studies, acute (24 hours or less) treatment with desipramine initially increased extracellular NE in the locus coeruleus by reuptake blockade (Mateo et al., 1998). This increase in NE was associated with α_2-adrenergic receptor mediated decreases in firing of locus coeruleus cells (Mateo et al., 1998; Svensson & Usdin, 1978) and decreased release of NE into the locus coeruleus terminal fields in cortex (Mateo et al., 1998). This decrease in firing of locus coeruleus cells persisted during subchronic (48 hours) treatment with desipramine (Linnér et al., 1999). In depressed patients following 48-hours of desipramine treatment, Veith et al. (1994) observed a short-term reduction in plasma NE accompanied by suppression of both the rates of extravascular and vascular NE appearance, which are compatible with a reduction in sympathetic nervous system activity.

Chronic antidepressant treatment in animals has been associated with reduced NE turnover in brain (as measured by reductions in brain deaminated catechol metabolites) and reduced levels of endogenous brain NE (Schildkraut et al., 1970 and 1971), as well as reduced expressions in brain of both the enzyme tyrosine hydroxylase (Nestler et al., 1990) and the presynaptic NE transporter protein (Bauer & Tejani-Butt, 1992).

However, chronic tricyclic antidepressant treatment is also associated with (i) a gradual reversal of the reduction in locus coeruleus firing during acute and subchronic (48 hour) treatment (Svensson & Usdin, 1978; Linnér et al., 1999; McMillen et al., 1980), (ii) a greater accumulation of NE in the cortical terminal fields of the locus coeruleus (Linnér et al., 1999; Mateo et al., 2001), and (iii) a gradual increase in the release and extraneuronal metabolism of NE in brain, as manifested by enhanced release of ^{3}H-NE, enhanced metabolism of ^{3}H-NE to ^{3}H-NMN, and an accumulation of ^{3}H-NMN in the presence of decreased levels of tritiated deaminated NE metabolites and endogenous brain NE (Schildkraut et al., 1970 and 1971). These findings during chronic treatment have been attributed to α_2-adrenergic desensitization (Svensson & Usdin, 1978; Linnér et al., 1999; McMillen et al., 1980); and significant desensitization of cortical α_2-adrenergic receptors has been observed in animals following long-term treatment with desipramine and other antidepressants (Mateo et al., 2001).

Veith et al. (1994) observed a rise in plasma NE after 4 weeks of desipramine treatment in depressed patients. Using an isotope-dilution, plasma NE kinetic technique, they attributed the increase in plasma NE concentrations to a progressive reduction in plasma NE clearance. In the present study, we were unable to measure plasma NE clearance based on the determination of plasma NE alone (Kopin et al., 1998). However, we did observe increases in plasma NE, 24-hour urinary NE, and 24-hour urinary NMN (the aminated O-methylated metabolite of NE)

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at Weeks 4 and 6 of desipramine treatment (see Tables 1 and 2), and (as indicated above) these changes at Weeks 4 and 6 were accompanied by persistent declines in 24-hour urinary measures of MHPG and VMA, which we first observed at Week 1 in this study (Table 1). Moreover, the present findings are compatible with the changes in NE metabolism Schildkraut et al. (1970 and 1971) observed in animal brain during chronic administration of tricyclic antidepressant drugs.

The increases in urinary NE and NMN levels at Weeks 4 and 6 are shown in Table 1. The increases at Weeks 4 and 6 in urinary NMN replicate earlier studies from our laboratory in which Schildkraut et al. (1966) observed gradual increases in levels of 24-hour urinary NMN (the metabolite of extraneuronal NE) during the period of definitive clinical improvement in depressed patients treated with imipramine. Taken together, our findings suggest the presence of an increase in the extraneuronal accumulation of NE during chronic desipramine treatment at a time when there is also a reduction in plasma NE clearance (Veith et al., 1994).

In healthy human subjects, Musso et al. (1992) observed increases in plasma DA levels during NE infusions in the presence of the α_2-adrenergic antagonist yohimbine. Since NE infusions reduced plasma DA levels in the absence of yohimbine, these authors proposed that this was mediated by an α_2-adrenergic mechanism. We observed increases in plasma DA levels after 4 and 6 weeks of desipramine treatment (Table 2). In accordance with the report of Musso et al. (1992), it is possible that these increases in plasma DA levels could reflect desensitization of α_2-adrenergic receptors during chronic desipramine treatment when urinary and plasma NE levels were elevated (Tables 1 and 2).

In the present study, there was no significant difference in urinary levels of E or MN, or in 8:00 a.m. plasma E, providing no evidence for an increase in E release accompanying the increase in extraneuronal NE release (see Results). Therefore, our findings of increases in urinary NE and NMN (Table 1) and 8:00 a.m. plasma NE (Table 2) reflect specific effects of chronic desipramine administration upon the noradrenergic neuronal system.

NE present in the synapse or extraneuronal spaces, which escapes reuptake by the NE transporter protein (Uptake 1) in the presynaptic noradrenergic neuron, can be taken up into adjacent glia (Russ et al., 1996) and neurons (Wu et al., 1998) in brain, or a broad range of tissues in the periphery (e.g., vascular and nonvascular smooth muscle; Martel & Azevedo, 2003) by a transmembrane protein (SL22A3) known as the extraneuronal monoamine transporter, the organic cation transporter type 3, or Uptake 2 (Burgen & Iversen, 1965; Gründemann et al., 1998; Wu et al., 1998).

Desipramine, which inhibits the NE transporter protein (Uptake 1), does not block the human extraneuronal monoamine transporter (Schömig & Schönfield, 1990). Following uptake into glia, postsynaptic neurons, or extraneuronal tissues by the extraneuronal monoamine transporter, NE is converted by catechol-O-methyltransferase to NMN. The efflux of NMN from the intracellular compartment appears to be independent of the extraneuronal monoamine transporter (Uhlig et al., 1976). Unlike desipramine, NMN is a potent inhibitor of the uptake of NE by the extraneuronal monoamine transporter (Burgen & Iversen, 1965), and the formation of NMN can reduce the uptake of NE by the extraneuronal monoamine transporter, thereby facilitating the increase in levels of NE in the synapse and other extraneuronal spaces. It is useful to note that patients with congestive heart failure have highly significant elevations of 24-hour urinary NE and NMN (Mäurer et al., 1976). Our analysis of the data reported by Mäurer et al. (1976) revealed that the ratio of 24-hour urinary NE/NMN was increased in patients with severe congestive heart failure when compared to healthy controls. Compatible with this increased ratio of NE/NMN, impairment in “whole-body Uptake 2” has been described in patients with this disorder (Leuenberger et al., 1992).

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In this study, we noted that the molar ratio of 24-hour urinary NE/NMN increased significantly at Weeks 4 and 6 of desipramine treatment, especially at Week 6 (see Results). As the levels of both urinary NE and NMN increased during treatment, these increases in the ratio of 24-hour urinary NE/NMN may reflect a reduction in the extraneuronal conversion of NE to NMN as time passed. These findings are compatible with the possibility that during chronic desipramine treatment, the conversion of NE to NMN is gradually reduced, in part, by the blockade of the extraneuronal monoamine transporter by the NE metabolite NMN. As noted above, this blockade of NMN would enhance extraneuronal levels of NE (see Tables 1 and 2).

Several limitations should be considered when interpreting our findings. The number of patients is small, but we had a low number of missing observations (less than 5%; see Results). Secondly, while we made every effort to collect information on the completeness of urine collections at the time of each visit, our results are limited by the actual compliance with the instructions given to each outpatient subject during their participation in this study. Thirdly, we did not employ repeated infusions of ^{3}H-NE in this research and so we could not directly study such parameters as the plasma clearance rate of NE (Veith et al., 1994) or the rate of NE entry into the extravascular compartment (Kopin et al., 1998) during our study. However, changes in plasma and 24 hr urinary catecholamines have mirrored changes in muscle sympathetic nerve activity in a variety of circumstances (Tataranni et al., 1999; Miyajima & Yamada, 1999; Miyajima et al., 2000), and changes in urinary NE and urinary NMN reflected increased plasma NE levels during infusions of NE into human subjects (Moleman et al., 1992).

Recently, another monoamine transporter, which is identified as the plasma membrane monoamine transporter or PMAT (a member of the SLC29 family; Engel et al., 2004; Zhou et al., 2007), has been found in the human central nervous system and spinal cord. PMAT shares several features with the extraneuronal monoamine transporter: both are low-affinity, high-capacity biogenic amine transporters which do not require either Na^{+} or $C1^{-}$ ions, and both are present in cells of neuronal or glial origin. PMAT has a significantly greater transport efficiency for serotonin than NE (Engel et al., 2004), while the extraneuronal monoamine transporter has a significantly greater transport efficiency for NE than for serotonin (Gründemann et al., 1998). The uptake by PMAT of NMN has not been described. It appears that the brain may employ a complex system of high-affinity (Uptake 1 or NET, SERT, and DAT) and low-affinity (the extraneuronal monoamine transporter and PMAT) transporters of biogenic amines to regulate the synaptic and extraneuronal concentration ranges of monoamine neurotransmitters such as NE and serotonin (Engel et al., 2004).

In summary, as noted above, during chronic treatment with desipramine, we suggest there is a blockade of the NE transporter protein (Uptake 1), increased accumulation of extracellular NE together with desensitization of alpha2-adrenergic receptors, and increased conversion of NE to NMN. Recently, we have hypothesized that the increase in NMN during chronic treatment with desipramine may block the extraneuronal uptake of NE (Uptake 2) to increase the levels of NE in the synapse, and this may be a crucial mediator of the clinical antidepressant effects of this drug (Schildkraut & Mooney, 2002 and 2004).

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TABLE 1

Changes in urinary catecholamines and metabolites during treatment with desipramine

Factor[a]	Baseline[a]	Week 1[a]	z, p[b]	Week 4[a]	z, p[b]	Week 6[a]	z, p[b]	Overall $X^{2[df=3]}$	Overall p[b]
NE	39±11	40±14	0.24,0.81	56±14[c]	3.37,0.001	52±20	2.27,0.023	14.3	0.002
NMN	238±86	216±85	−1.49,0.13	284±95[c]	2.58,0.010	275±117	2.15,0.032	11.5	0.009
MHPG	2091±622	1752±494	−4.12,<0.001	1856±506	−2.39, 0.017	1723±522	−3.15,0.002	20.9	0.001
VMA	3670±579	2865±530	−9.48,<0.001	3006±641[c]	−4.37,<0.001	3061±742	−3.33,0.001	92.4	<0.001

[a] All values are presented as means ± 1SD and expressed in micrograms per 24 hr. NE=norepinephrine; NMN=normetanephrine; MHPG=3-methoxy-4-hydroxyphenylglycol; VMA=vanillylmandelic acid.

[b] Z-statistic and p-value determined by random effects regression modeling methods, with time-in-weeks as the explanatory factor.

Cell counts are 15 for most cells, with the exception of: c=14.

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TABLE 2

Changes in plasma catecholamines and metabolites during treatment with desipramine

Factor[a]	Baseline[a]	Week 1[a]	z, p[b]	Week 4[a]	z, p[b]	Week 6[a]	z, p[b]	Overall $X^{2[df=3]}$	Overall p[b]
NE	0.421±0.153[c]	0.415±0.103[d]	−0.17,0.28	0.571±120[e]	3.37,<0.001	0.635±0.169[c]	3.61,<0.001	25.0	<0.001
MHPG	3.5±0.68[c]	2.5±0.47[d]	−5.94,<0.001	2.7±0.90[e]	−3.10, 0.002	2.6±0.70[e]	−4.36,<0.001	35.7	<0.001
DA	0.030±0.014[c]	0.035±0.016[d]	0.79,0.43	0.049±0.027[e]	2.52,0.012	0.055±0.038[c]	2.34,0.019	9.5	0.024

[a] All values are presented as means ± 1SD and expressed in nanograms per ml. NE=norepinephrine; MHPG=3-methoxy-4-hydroxyphenylglycol; DA=dopamine.

[b] Z-statistic and p-value are determined by random effects regression modeling methods, with time-in-weeks as the explanatory factor.

Cell counts are indicated as follows: c=13, d=12, e=11.