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Effects of Risperidone on the Peripheral Noradrenegic System in Patients with Schizophrenia: A Comparison with Clozapine and Placebo

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Risperidone is an atypical antipsychotic drug that increases plasma norepinephrine (NE) levels, but the mechanism behind this effect is unclear. We measured arterial plasma levels of NE and other catechols during intravenous infusion of tritium-labeled NE (^{3}H-NE) in risperidone-treated patients and compared their data with those from patients treated with clozapine or placebo. NE levels in risperidone patients were significantly higher than in placebo patients, but lower than in clozapine patients. Neither drug, however, had significant effect on plasma levels of the main neuronal metabolite of NE, dihydroxyphenylglycol (DHPG), suggesting that adrenoceptors blockade alone would not explain the NE findings. The rate of release of endogenous NE into the bloodstream (spillover) was elevated in both risperidone and clozapine patients in a manner that paralleled their NE levels; the NE clearance in both groups did not differ from placebo. Following ^{3}H-NE infusion in risperidone-treated individuals, production of ^{3}H-DHPG was normal, as it was in the clozapine group, suggesting that risperidone does not impede neuronal uptake or intraneuronal metabolism of NE by monoamine oxidase. Our data suggest that both risperidone and clozapine elevate plasma NE levels via enhanced neurotransmitter spillover, with risperidone producing a smaller effect.

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Clozapine is an atypical antipsychotic drug (APD) with efficacy superior to that of conventional agents and with little or no extrapyramidal signs or symptoms (EPS) (Kane et al. 1988; Lieberman et al. 1989; Breier et al. 1994a; Meltzer 1995; Meltzer et al. 1996). Because these advantageous therapeutic properties are accompanied by unusually severe side effects, scientists have been searching for clozapine-like APDs that would share its beneficial features but not induce bone marrow toxicity, seizures, or hypotension. This search has resulted in the introduction of four "newer atypical APDs" (i.e., risperidone,

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olanzapine, quetiapine, and ziprasidone), all of which have important effects on both dopaminergic and serotonergic neurotransmitter systems. Because none of these compounds has been proven as efficacious as the prototype, clozapine, in the treatment of resistant cases, continued research is focusing on other neurotransmitter systems affected by clozapine.

Clozapine profoundly increases norepinephrine (NE) levels in both CSF (Ackenheil 1989; Lieberman et al. 1989; Lieberman et al. 1991; Pickar et al. 1992) and plasma (Pickar et al. 1992; Green et al. 1993; Davidson et al. 1993; Breier 1994; Breier et al. 1994b; Schulz et al. 1996; Schulz et al. 1997; Brown et al. 1997; Fleischhaker et al. 1998; Elman et al. 1999), an effect not seen with typical APDs. In some (Breier et al. 1994b; Schulz et al. 1997; Fleischhaker et al. 1998), but not all (Brown et al. 1997) studies, plasma NE increases have been related to clinical improvement, suggesting that this pharmacological effect may play a role in clozapine's beneficial central actions. In this context, findings implicating noradrenergic dysregulation in the pathophysiology of schizophrenia (Stein and Wise 1971; Sternberg 1984; Breier et al. 1990; Rao and Moller 1994; Breier 1994; Yamamoto et al. 1994; Litman et al. 1996; Breier et al. 1998; Goff and Evins 1998; Friedman et al. 1999a; Friedman et al. 1999b; Klimek et al. 1999) further support inquiry into the relevance of noradrenergic mechanisms in the action of APDs.

We have reported previous data suggesting that high plasma NE levels in clozapine-treated patients result from increases in the appearance rate of the endogenously released NE in the plasma (spillover) rather than from decreased neuronal uptake of NE, inhibition of intraneuronal monoamine oxidase (MAO), or adrenoceptor antagonism (Elman et al. 1999). Risperidone, the next atypical antipsychotic drug marketed in the United States after clozapine, is associated with a low incidence of EPS and may have improved efficacy compared with conventional agents (Kane and McGlashan 1995; Pickar 1995; Campbell et al. 1999). Interestingly, risperidone has also recently been observed in a clinical study to produce a modest (i.e., 58%) increase in plasma NE levels (See et al. 1999), thus extending the phenomenon of NE elevations to another atypical APD.

Although both risperidone and clozapine appear to share an ability to produce elevations of plasma NE, there are striking differences in their neurochemical properties. Even though both agents have a high serotonin $5HT_{2A}$-to-dopamine D_2 binding ratio (a characteristic shared by most atypicals), risperidone has two orders of magnitude higher affinity for both of these receptors than does clozapine; it also has a substantially higher affinity for α_1 and α_2 adrenoceptors than does clozapine (Schotte et al. 1993; Breier et al. 1999; Richelson 1999). Also, among atypical APDs, risperidone has the simplest binding profile and clozapine has the most broad-spectrum one (Stahl 2000).

The differences in the receptor binding profiles of these two compounds led us to wonder whether the reportedly modest NE elevation produced by risperidone (See et al. 1999) was generated by the same mechanism that results in a profound (i.e., 200–400%) NE elevation in patients treated with clozapine. To explore this issue, we applied a comprehensive neuropharmacological approach that includes intravenous infusion of tracer amounts of tritium-labeled NE (^{3}H-NE) in schizophrenic patients treated with risperidone. Because formation of ^{3}H-dihydroxyphenylglycol (DHPG) from ^{3}H-NE requires both neuronal uptake and intraneuronal deamination by MAO, measurement of plasma ^{3}H-DHPG responses furnished the basis for examining the effects of risperidone. Plasma levels of the NE precursor, dihydroxyphenylalanine (DOPA), and of the dopamine metabolite, dihydroxyphenylacetic acid (DOPAC), were also measured to provide information about NE synthesis (Goldstein et al. 1987; Goldstein 1995) and about intraneuronal metabolism by monoamine oxidase (MAO; Goldstein 1995).

Our previous work suggested that clozapine has complex effects on the noradrenergic system, producing a robust increase in NE, but without an expected proportional increase in DHPG (Breier et al. 1994b; Elman et al. 1999). We hypothesized, based on the receptor binding profile of risperidone, that patients treated with the drug would display different characteristics of the noradrenergic response than their clozapine-treated counterparts. Specifically, risperidone's very potent antagonism at the α_1 and α_2 adrenoceptors (Schotte et al. 1993; Richelson 1999) was expected to increase sympathetic outflow, caused by vasodilatation (from α_1 effects) and blockade of inhibitory α_2 adrenoceptors on sympathetic nerves, thus producing high NE spillover. This would be combined with heightened intraneuronal NE metabolism and production of DHPG, as adrenoceptor blockade usually produces increases in DHPG plasma levels that parallel the NE increases (Breier 1994; Goldstein 1995).

MATERIALS AND METHODS

Subjects

Eight risperidone-, twelve clozapine- and six placebo-treated patients with schizophrenia who participated in this research protocol were enrolled in the double blind, parallel group comparative efficacy study of the effects of risperidone and clozapine (Breier et al. 1999) at the Section on Clinical Studies, National Institutes of Health (NIH) Clinical Center, Bethesda, MD. Data from clozapine- and placebo-treated patients have been previously reported (Elman et al. 1999) and are included in this article to allow for comparison with the risperidone effects. All subjects gave written informed consent to

participate in the protocol, which was approved by the NIH IRB. All subjects were in good physical health as evidenced by physical examination, ECG, and screening blood tests. Patients with concurrent drug abuse, alcoholism, organic brain disorder, mental retardation, or a medical condition that contraindicates use of risperidone or clozapine were excluded from the study. The treatment groups did not differ in demographic or clinical characteristics (Table 1). The patients were on a stable dose of medication or placebo for a 2-week minimum prior to the study; they did not receive other medications. Doses had been varied to achieve maximal clinical efficacy (risperidone mean dose ± SD: 3.9 ± 1.9 mg per day; clozapine mean dose ± SD: 390.0 ± 188.3 mg per day).

Procedure

The subjects were studied at 9 am after having fasted and refrained from alcohol, tobacco, caffeine, or physical activity for at least 10 h. With the patient in supine position, an arterial catheter was inserted percutaneously after local anesthesia of the overlying skin. An antecubital IV catheter was inserted into the contralateral arm. After 60 min of resting, ^{3}H-NE ([1,7-^{3}H]NE, 14-22 Ci/mmol; New England Nuclear, Boston, MA) in 50 ml normal saline was infused intravenously at 0.75 ml/min. Arterial blood samples (7–8 ml) were obtained at 15, 30, 45, and 60 min after the ^{3}H-NE infusion began.

Biochemical Variables

Blood for assays was collected in heparinized tubes and placed on wet ice. After separation by refrigerated centrifugation, the plasma was stored at -80°C. Plasma catechol levels were assayed using liquid chromatography with electrochemical detection (Eisenhofer et al. 1986). Concentrations of ^{3}H-NE and ^{3}H-DHPG were measured by scintillation spectrometry on effluent from the chromatographic column (Eisenhofer et al. 1991). Inter-assay coefficients of variation were 6.5% for NE, 3.9% for ^{3}H-NE, 8.4% for DHPG, 4.7% for ^{3}H-DHPG, 5.9% for DOPA, and 11.6% for DOPAC. Intra-assay coefficients of variations were 1.9% for NE, 3.2% for ^{3}H-NE, 3.7% for DHPG, 7.6% for ^{3}H-DHPG, 3.8% for DOPA, and 3.9% for DOPAC.

The rate of release of endogenous NE into arterial plasma and the rate of clearance from plasma was determined with the following equations: 1) CL=IR/[^{3}H]-NE and 2) SP=CLxNEa; where CL is the arterial plasma NE clearance (ml/min), IR is the infusion rate of [^{3}H]-NE, [^{3}H]-NE is the arterial plasma concentration of [^{3}H]-NE, SP is the NE spillover rate (pmol/min) into arterial plasma, and NEa is the arterial plasma concentration of endogenous NE (Esler et al. 1979). Neuronal uptake (Eisenhofer et al. 1991) and NE stores at the active release sites (Eisenhofer et al. 1991; Eisenhofer et al. 1996) were assessed from the ^{3}H-DHPG and ^{3}H-NE concentrations.

Statistical Analyses

The data were analyzed using Statistica (StatSoft, Inc., Tulsa OK). Because no time-related changes were expected for the non tritium-labeled neurochemicals, their measurements across the four sampling points were averaged and expressed as means ± standard deviation (SD). Differences among the treatment groups were assessed by one-way analysis of variance (ANOVA), with drug condition (risperidone, clozapine, and placebo) as the grouping factor. When a group effect was significant, post-hoc *t*-tests were performed. Time-related trends in ^{3}H-DHPG/^{3}H-NE ratios were examined by repeated-measures ANOVAs, with drug condition as the grouping factor and time as the within-subjects factor. A p value of less than 0.05 defined statistical significance. All tests were two-tailed.

RESULTS

Catechol Levels

Both risperidone- and clozapine-treated groups had elevated plasma NE levels, averaging respectively almost two and four times higher than the placebo-treated group ($F=9.89$; $df=2,23$; $p < .001$; Figure 1). Post-hoc *t*-tests revealed significantly lower NE levels in risperidone- versus clozapine-treated ($t=-2.64$; $df=18$; $p = .02$) patients, and significantly higher NE levels in risperidone- versus

Table 1. Demographic and Clinical Characteristics of Schizophrenic Patients Treated with Clozapine, Risperidone, and Placebo.

Patient Characteristic	Clozapine	Risperidone	Placebo	F (df=2,23); p
Age (years)	36.0 (8.4)	37.9 (9.7)	42. 7 (4.7)	1.32; 0.29
Sex (M/F)	10/2	7/1	4/2	—
Age of onset (years)	21.6 (4.3)	23.9 (7.4)	27.8 (6.0)	2.34; 0.12
No. of hospitalizations	5.3 (7.5)	7.5 (4.6)	2.7 (2.4)	1.35; 0.28

Data are presented as mean (SD).
Clozapine (N = 12); risperidone (N = 8); placebo (N = 6).

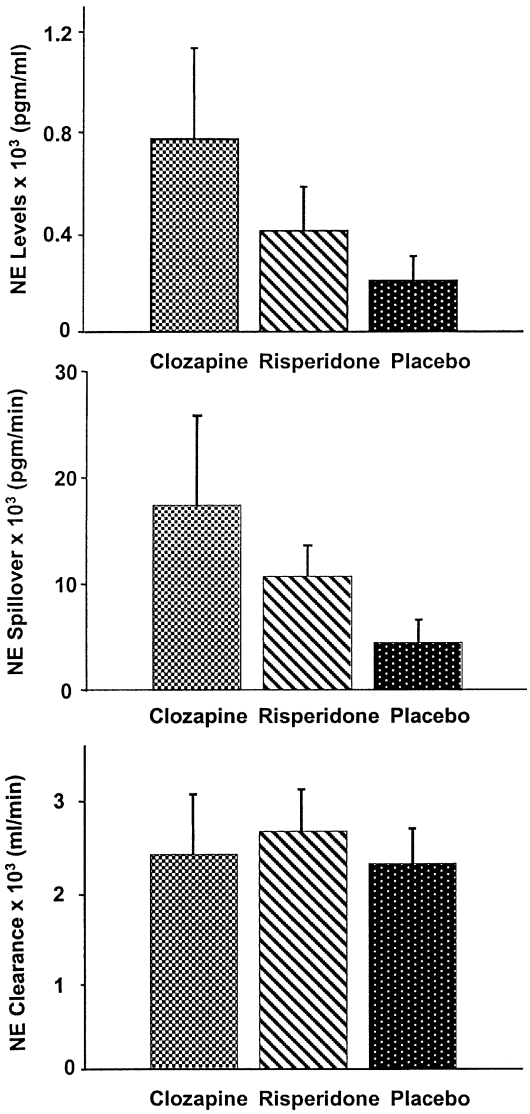

Figure 1. NE plasma level, NE spillover, and NE clearance in schizophrenic patients treated with clozapine (n = 12), risperidone (n = 8), and placebo (n = 6). Data are presented as mean±SD. Statistical differences were determined using a one-way analysis of variance (ANOVA) with drug condition (risperidone, clozapine, and placebo) as the grouping factor and post-hoc *t*-tests. Significant effect for both plasma NE levels ($F=9.89$; $df=2,23$; $p < .001$) and NE spillover ($F=9.65$; $df=2,23$; $p = .001$), but not for NE clearance ($F=0.87$; $df=2,23$; $p = .43$). Significantly lower NE levels in risperidone- vs. clozapine-treated ($t=-2.64$; $df=18$; $p = .02$) patients, and significantly higher NE levels in risperidone- vs. placebo-treated ($t=2.64$; $df=12$; $p = .02$) individuals. Significantly lower NE spillover values in risperidone- vs. clozapine-treated ($t=-2.37$; $df=18$; $p = .03$) group, and significantly higher values in risperidone- vs. placebo-treated ($t=3.91$; $df=12$; $p < .01$) group.

placebo-treated ($t=2.64$; $df=12$; $p = .02$) individuals. Mean plasma DHPG levels were 24% higher (trend significance; $t=1.72$; $df=18$; $p = .1$) in risperidone- versus clozapine-treated patients and 15% higher (not significant) in risperidone- versus placebo-treated patients (Table 2). The groups did not differ in plasma levels of DOPA and DOPAC.

NE Spillover

There was a significant drug condition effect on NE spillover ($F=9.65$; $df=2,23$; $p = .001$; Figure 1). Post-hoc *t*-tests revealed significantly lower NE spillover values in risperidone- versus clozapine-treated ($t=-2.37$; $df=18$; $p = .03$) group and significantly higher values in risperidone- versus placebo-treated ($t=3.91$; $df=12$; $p < .01$) group.

NE Clearance

The three treatment groups did not differ in plasma NE clearance ($F=0.87$; $df=2,23$; $p = .43$; Figure 1).

Time-Related Trends in ^{3}H-DHPG/^{3}H-NE Ratio

^{3}H-DHPG/^{3}H-NE ratios increased progressively with time ($F=12.72$; $df=3,69$; $p < .0001$). The increases did not differ among the groups, as indicated by a statistically non-significant interaction effect for group with time ($F=0.09$; $df=3,69$; $p = 1.0$; Figure 2).

DISCUSSION

In this study, risperidone produced substantial increases in arterial plasma NE levels, reflecting enhanced NE spillover. Furthermore, our data show that risperidone differs from clozapine in some of its noradrenergic effects. Risperidone-treated patients displayed plasma NE concentrations that were lower than those of clozapine- but higher than placebo-treated patients. By contrast, the DHPG levels of risperidone patients were actually 24% higher (trend significance) as compared with patients on clozapine. On the other hand, as with clozapine, risperidone did not alter DOPA and DOPAC levels, or the time-related changes in the ^{3}H-DHPG/^{3}H-NE ratio following ^{3}H-NE infusion.

Although some prior clinical studies support the noradrenergic system's involvement in the treatment response to clozapine (Breier et al. 1994b; Schulz et al. 1997; Fleischhaker et al. 1998), no such data are available for risperidone (See et al. 1999), and no inferences can be made about risperidone's therapeutic mechanisms of action from this investigation that was primarily focused on its pharmacokinetic effects. Nonetheless, peripheral NE measures are important because a considerable amount of animal data, where peripheral and central measures were collected simultaneously in the presence of an effective blood-brain barrier, suggest that plasma measures may reflect directionally similar changes in the brain (Ziegler et al. 1977; Jimerson et al.

Table 2. Arterial Plasma Catechol Levels (pgm/ml) in Schizophrenic Patients Treated with Clozapine, Risperidone, and Placebo.

Catechol	Clozapine	Risperidone	Placebo	F (df=2,23); p
DHPG	727.85 (172.89)	903.72 (286.71)	783.88 (186.78)	1.59; 0.22
DOPA	1527.19 (271.27)	1407.47 (344.56)	1403.79 (282.70)	0.54; 0.59
DOPAC	1104.08 (224.21)	1238.91 (484.83)	1398.92 (532.10)	1.13; 0.34

Data are presented as mean (SD).
Clozapine (N = 12); risperidone (N = 8); placebo (N = 6).

1981; Lambert et al. 1997; Esler et al. 1998; Tjurmina et al. 1999). Hence, changes in plasma NE in risperidone-treated patients may suggest analogous changes in the patients' brain (Breier 1994; Breier et al. 1994b; Brown et al. 1997). In addition, peripheral effects of NE alone could be hypothesized to contribute to potential adverse outcomes. For instance, given preclinical (Nagai et al. 1995) and clinical (Walters et al. 1997) evidence suggesting NE's anti-insulin activity, this effect may be involved in the development of diabetic ketoacidosis reported during treatment with both atypical agents (Colli et al. 1999; Croarkin et al. 2000).

Our findings are consistent with the previous report of risperidone-induced plasma NE elevations (See et al. 1999). The almost two-fold increase that we noted was unexpected, given that the previous study found modest increases that averaged 58% (See et al. 1999). Direct comparison between See et al. (1999) and our study, however, is complicated by methodological differences. The former study (See et al. 1999) involved within group comparison of NE levels from blood; our study used between group comparison of arterial plasma NE levels. In particular, the differences in the source of the NE sample may be crucial because NE concentrations in antecubital venous blood may be unreliable indicators of total body sympathetic nervous activity (Folkow et al. 1983). An advantage of arterial sampling is independence from local peripheral metabolism and blood flow, as suggested by studies demonstrating that tissues of the arm remove a substantial proportion of the radioactively-labeled NE in the arterial plasma (Chang et al. 1986).

Even though our previous study showed that α_2 blockade alone would not explain the patterns of cloza-

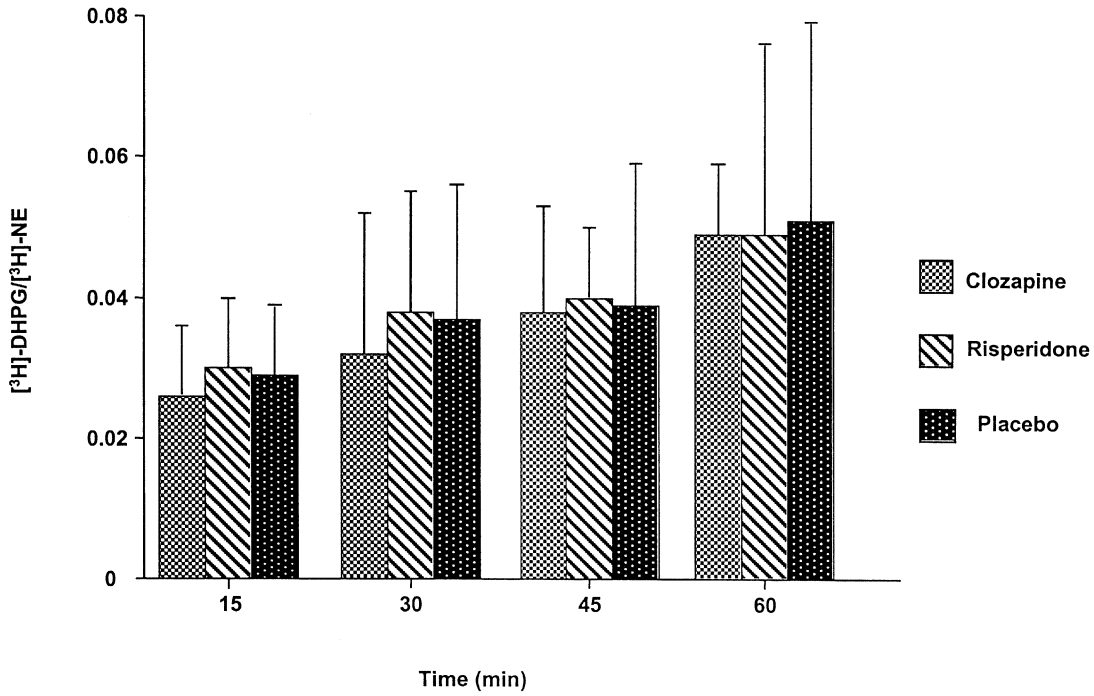

Figure 2. ^{3}H-DHPG/^{3}H-NE ratio in schizophrenic patients treated with clozapine (n = 12), risperidone (n = 8), and placebo (n = 6). Data are presented as mean±SD. Time-related trends in ^{3}H-DHPG/^{3}H-NE ratios were examined by repeated-measures ANOVAs, with drug condition (risperidone, clozapine, and placebo) as the grouping factor and time (15, 30, 45, and 60 min) as the within-subjects factor.

pine-induced sympathetic stimulation (Elman et al. 1999), we hypothesized that this mechanism would have more prominence in risperidone-treated patients because of risperidone's high affinity for α_2 adrenoceptors (Schotte et al. 1993). Despite this, we observed substantial increases in plasma NE in patients treated with risperidone without corresponding changes in DHPG, as compared with patients on placebo ($t=0.89$; $df=12$; $p = .40$), leading us to conclude that (like clozapine) α_2 blockade alone could not be the sole explanation for risperidone's noradrenergic effects (Nasif et al. 2000). This is because plasma DHPG levels generally parallel NE levels during sympathetic stimulation (caused by α_2 blockade), because of increased reuptake of the released NE.

In this study, NE spillover was increased in risperidone-treated patients, although less dramatically than in those treated with clozapine. Several factors determine NE spillover, besides exocytotic release in response to sympathetic nerve traffic. Probably, the most important is neuronal reuptake. Estimates of the efficiency of reuptake of endogenously released NE range up to about 90% (Iversen 1973; Esler et al. 1990). Clearly, even a small amount of inhibition of reuptake would augment the amount of NE entering the plasma for a given rate of exocytotic release from the terminals. The finding of high plasma NE levels in patients treated with risperidone without a corresponding increase in plasma DHPG would suggest that impaired NE reuptake might be involved in the NE increase, because plasma DHPG reflects the metabolism of axoplasmic NE (Goldstein et al. 1988; Goldstein 1995). All other things being the same, decreased reuptake of NE would increase NE spillover but decrease plasma DHPG levels. Moreover, risperidone has been demonstrated in preclinical studies to exert some degree of NE uptake inhibition (Leysen et al. 1988; Yoshimura et al. 2000). Thus, in this study, we explored the issue of possible neuronal uptake blockade by risperidone.

Neuronal reuptake contributes to clearance of circulating NE in humans (Esler et al. 1981; Eisenhofer et al. 1991). The present finding of no change in NE clearance in risperidone-treated patients compared with those on placebo argues against inhibition of neuronal uptake as a basis for high plasma NE levels in these patients. To examine neuronal uptake more specifically, we measured the arterial plasma ^{3}H-DHPG response during ^{3}H-NE infusion. Production of ^{3}H-DHPG in patients on risperidone was similar to what was found in patients on placebo and those treated with clozapine, with or without correction of ^{3}H-DHPG levels for concurrent plasma ^{3}H-NE levels. As ^{3}H-DHPG production in this setting results virtually exclusively from metabolism of ^{3}H-NE in the sympathetic axoplasm (Goldstein et al. 1988; Goldstein 1995), the finding of normal ^{3}H-DHPG and ^{3}H-DHPG/^{3}H-NE ratio responses would appear to eliminate decreased neuronal reuptake as the mechanism of high plasma NE levels in risperidone-treated patients.

A buildup of NE in the axoplasm, such as by inhibition of MAO and of the vesicular monoamine transporter, could increase NE release by a non-exocytotic process, via exit through the membrane transporter (Eisenhofer et al. 1986; Hovevey-Sion et al. 1990). The present finding of normal plasma levels of ^{3}H-DHPG following ^{3}H-NE infusion in risperidone-treated subjects renders MAO inhibition a highly unlikely mechanism of action of risperidone. Moreover, blockade of the vesicular monoamine transporter accelerates the rate of attainment of plateau ^{3}H-DHPG concentrations during ^{3}H-NE infusion (Eisenhofer et al. 1991), and in the present study risperidone treatment did not alter the slowly progressive increase in plasma ^{3}H-DHPG levels.

Finally, although theoretically blockade of extraneuronal uptake of catecholamines or of the extraneuronal metabolizing enzyme catechol-O-methyltransferase could increase plasma NE levels for a given rate of entry into the interstitial fluid, too little of endogenously released NE undergoes extraneuronal uptake and enzymatic O-methylation to explain the two-fold increase in plasma NE levels in risperidone-treated subjects (Lenders et al. 1992; Lenders et al. 1993).

In conclusion, the pilot data presented here suggest that two second-generation APDs, risperidone and clozapine, share both similarities and differences with regard to their noradrenergic effects. Both drugs elevate plasma NE levels. Risperidone, as compared with clozapine, produces smaller elevations in arterial plasma NE secondary to lesser increases in NE spillover. At the same time DHPG levels tend to increase in risperidone- and to decrease in clozapine-treated patients. Differences in other indices of the noradrenergic system such as NE clearance, reuptake, and synthesis as well as MAO activity are not obvious. These data call for further research aimed at understanding the distinctive features of clozapine's noradrenergic effects vis-à-vis those of risperidone and their potential role in the drug's unique therapeutic profile.

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