

Reduced Brain Norepinephrine and Dopamine Release in Treatment-Refractory Depressive Illness

Evidence in Support of the Catecholamine Hypothesis of Mood Disorders

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Background: The etiology of depressive illness has been linked with brain monoaminergic neuronal dysfunction, yet the development of sensitive markers of endogenous depression has proven difficult.

Methods: Using catheters placed in an internal jugular vein, we estimated the release of brain monoamine neurotransmitters in 19 healthy volunteers and in 9 patients with nonbipolar depressive illness refractory to medication at rest and following intravenous desipramine hydrochloride. Venoarterial plasma concentration gradients were used to quantify the amount of neurotransmitters stemming from the brain. Cerebral oxidative metabolism was assessed concurrently from measurements of oxygen and carbon dioxide gas exchange via the process of regional indirect calorimetry.

Results: The brains of these patients exhibited reduced venoarterial norepinephrine (4.0 ± 2.7 nmol/L vs 0.7 ± 1.3 nmol/L) and homovanillic acid concentration gradients (8.3 ± 7.8 nmol/L vs 3.1 ± 1.9 nmol/L), and used an en-

ergy source other than glucose. Internal jugular 5-hydroxyindoleacetic acid concentration gradients were not reduced in the patients with depressive illness. While both the reduction in norepinephrine turnover and the defect in cerebral metabolism were normalized following pharmacological blockade of the norepinephrine transporter with desipramine, paradoxically it was the brain's turnover of dopamine that bore a significant relation to the patients' clinical status ($r_s = 0.79$, $P = .02$). The positive nature of this relationship remains difficult to reconcile.

Conclusions: In accordance with the monoamine hypothesis, a deficit in brain norepinephrine and dopamine exists in patients with depressive illness. Moreover, the brains of these patients use an energy source other than glucose, a situation that is normalized following the acute pharmacological blockade of the norepinephrine transporter with the tricyclic antidepressant, desipramine.

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THE DEBILITATING symptoms that accompany bouts of depressive illness are presumed to arise, at least in part, because of an aberration in brain monoamine neuronal activity. The effectiveness of certain antidepressant medications, such as norepinephrine uptake-blocking agents, formed the foundation for the catecholamine deficiency hypothesis of affective disorders.¹ The observation that a substantial proportion of patients with depression fail to respond to available medications suggests that it is implausible to ascribe the symptoms of depression merely in terms of abnormal brain noradrenergic neuronal activity. Niklasson and Ågren² have documented weak monoaminergic neurotransmission in

patients with depression and have demonstrated an association between diminished brain monoaminergic function and reduced cerebral metabolism.

Examination of peripheral indices of monoaminergic function in depressive illness has yielded disparate results. Some studies³⁻⁶ indicate a tendency for both the urinary excretion level and cerebrospinal fluid level of norepinephrine and its metabolites to be diminished in patients with depression. Other reports document elevated plasma levels of norepinephrine⁷ and increased rates of norepinephrine spillover to plasma^{8,9} in such patients. The observation that cerebrospinal fluid homovanillic acid (HVA) levels are reduced in patients with depression¹⁰ and in depressed suicide attempters, but not in those nonde-

SUBJECTS AND METHODS

SUBJECTS

Data obtained from 9 medication-free patients with mood disorders (6 male, 3 female; mean \pm SD age, 47 \pm 2 years; mean \pm SD body mass index [calculated as weight in kilograms divided by the square of height in meters], 27.1 \pm 2.2) and 19 healthy subjects of similar age (16 male, 3 female; age, 45 \pm 3 years, body mass index, 25.3 \pm 0.7) form the basis for this report. The patients were consecutive admissions to a special inpatient protocol, who consented to the proposed catheterization procedure. The Sahlgrenska University Hospital Ethics and Isotope Committees (Gothenburg, Sweden) approved the protocol presented. All patients and volunteers gave written informed consent prior to their participation in the procedure.

The patients were referred from local psychiatric outpatient services for clinical investigation of depression refractory to ordinary pharmacological treatments. Patients were admitted to a psychiatric research ward of Sahlgrenska University Hospital at Mölndal for a 5-day period. They were evaluated using the Schedule for Affective Disorders and Schizophrenia (SADS)^{18,19} and underwent biochemical evaluation of brain monoaminergic neuronal activity as part of an extensive psychobiological investigation. Eight patients fulfilled *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for a current unipolar major depression and 1 fulfilled *DSM-IV* criteria for current dysthymia. The patients did not fulfill the criteria for other concomitant psychiatric disorders and none of the patients had a present or past substance abuse disorder. No patient had received psychotropic medication for at least 20 days prior to their admission (**Table 1**). In patients 2 and 5, fluoxetine therapy ceased 28 and 30 days, respectively, prior to catheterization. One patient had a history of hypertension but was not taking any centrally acting antihypertensive medications. Catheter studies were performed during the morning of the final day of the patients' stay in hospital.

Prior to their acceptance in the experimental protocol, the healthy subjects were recruited through a local advertisement and underwent comprehensive clinical and physical examinations to screen for previously undiagnosed medical conditions. Exclusion criteria included any history of major illness, previous psychiatric therapy, cardiovascular disease, and current drug medication.

CEREBRAL BLOOD FLOW SCAN

Prior to the catheter procedure, each subject underwent a cerebral blood flow scan to ascertain the route of drainage of the superior sagittal sinus²⁰ (**Figure 1**), thereby

permitting, to a degree, the differentiation between cortical and subcortical cerebral venous drainage. It has been proposed that altered noradrenergic innervation from the locus coeruleus in depressive illness leads to dysregulation of both serotonergic and dopaminergic neurotransmission.²¹ Given the apparent importance of the locus coeruleus, an area accounting for no less than 50% of norepinephrine in the brain²² in depression, we chose to sample from the internal jugular vein that drains the subcortical brain regions. This blood vessel also carries the majority of brain HVA,²³ the principal metabolite of dopamine in the brain.

Cerebral blood flow scans were performed at the Sahlgrenska University Hospital's Division of Nuclear Medicine using a technique based on previously described methods.²³ In brief, 2 mL to 3 mL of blood was obtained from the subjects and the red blood cells labeled with technetium. The radioactively tagged blood cells were then reinjected into the subject and the scintigraphic image monitored.

CATHETER PROCEDURE

Catheter studies were performed in the morning with subjects in the supine position. Caffeinated beverages, alcohol, and tobacco smoking were prohibited for the 12 hours preceding the study. Blood samples were obtained simultaneously from internal jugular venous and brachial artery catheters percutaneously inserted under strict aseptic conditions.²³ The internal jugular venous catheter was advanced beyond the mandibular angle upstream to points of entry of veins draining the face and neck to minimize any contamination of the cerebral venous effluent. The catheter was used for sampling blood from the internal jugular vein. Throughout the studies, levo-[7-³H]-norepinephrine (specific activity 40.7 \times 10¹⁰ Bq to 92.5 \times 10¹⁰ Bq; New England Nuclear, Boston, Mass) was infused into the subjects via a peripheral vein for assessing the transcerebral extraction of norepinephrine and the rate of total-body spillover of norepinephrine into plasma.^{24,25} Tritium-labeled epinephrine (levo-[N-methyl-³H]-epinephrine, specific activity 255.3 \times 10¹⁰ Bq to 288.6 \times 10¹⁰ Bq; New England Nuclear) was also infused to measure the rates of epinephrine secretion.²⁶

After control blood samples had been obtained in the patients with depressive illness, an intravenous infusion of the tricyclic antidepressant desipramine hydrochloride was commenced. The drug was given slowly, yielding a total dose of 3 mg/kg after 30 minutes. Blood sampling for cerebral neurochemical evaluation was performed at rest and 30 minutes after the initial desipramine administration; blood gas and glucose analysis was performed at rest and at 15 minutes and 30 minutes after desipramine administration. Plasma neurochemical, blood gas, hemoglobin, and glucose analyses were performed using previously described methods.²⁷

pressed suicide attempters,¹¹ implicates dopamine in the etiology of depressive illness.¹² A major drawback in using urinary concentrations, or for that matter peripheral plasma levels of a particular neurotransmitter as an indicator of brain neuronal dysfunction is that there exist multiple sites of production of these compounds outside the central nervous system.¹³⁻¹⁵ Whether lumbar cerebrospinal fluid concentrations are a reliable indica-

tor of brain neurotransmitter turnover is also open to conjecture.

To circumvent these problems, we used percutaneously placed catheters high in an internal jugular vein to measure the venoarterial concentration gradient of central nervous system monoamine neurotransmitters, and to examine their relation to cerebral metabolism in patients presenting with nonbipolar depressive mood dis-

NEUROCHEMICAL DETERMINATION

In primates, 3-methoxy-4-hydroxyphenylglycol (MHPG) and HVA are the principal metabolites of norepinephrine and dopamine released from the brain into the blood.²⁸ Conjugation is of minimal importance in the disposition of these neurotransmitters. The metabolism of serotonin is achieved almost exclusively via the actions of monoamine oxidase and aldehyde dehydrogenase, resulting in the formation of 5-hydroxyindoleacetic acid (5-HIAA). Plasma neurochemical concentrations were determined by high-performance liquid chromatography coupled with coulometric detection.^{27,29} Timed collection of ³H-eluate leaving the coulometric cell permitted separation of the ³H-norepinephrine and epinephrine for subsequent counting by liquid scintillation spectroscopy. Interassay coefficients of variation were 4.6% and 10% for endogenous norepinephrine and epinephrine respectively, and 3.2% and 7% for ³H-norepinephrine and ³H-epinephrine, respectively. Intra-assay coefficients of variation were 2% and 10% for endogenous norepinephrine and epinephrine, respectively, and 3% for both ³H-norepinephrine and ³H-epinephrine. The interassay coefficients of variation for MHPG, dihydroxyphenylglycol (DHPG), HVA, and 5-HIAA were $\pm 4\%$, $\pm 8\%$, $\pm 5\%$ and $\pm 6\%$, respectively. The intra-assay coefficients of variation for these compounds were $\pm 4\%$, $\pm 2\%$, $\pm 2\%$, and $\pm 2\%$, respectively. All assays were linear within the physiological range, with a sensitivity (signal-noise ratio of 3) of 0.1 pmol/L for norepinephrine, epinephrine and DHPG, 0.3 pmol/L for HVA and 5-HIAA and 1.0 pmol/L for MHPG.

CALCULATIONS

Cerebral Monoamine Release

The kinetics of microcirculatory exchange are well-established, with concentrations at the venous end of the circulation being largely determined by concentrations in the interstitial compartment.³⁰ Venoarterial plasma concentration differences were used as indicators of neuronal activity. For the catecholamine norepinephrine, a further adjustment was made allowing for the fractional extraction of ³H-labeled catecholamine across the brain.³¹ As there is no evidence of extraction of DHPG during transcerebral passage,³² internal jugular venous DHPG increments were calculated without recourse to isotope dilution methodology. MHPG is relatively nonpolar and is able to diffuse across the blood-brain barrier.³³ In studies performed by Kopin et al,³⁴ at steady state there occurs a slow but free exchange of plasma and cerebrospinal fluid MHPG. Although isotope dilution methods were not relied on in our estimation of brain MHPG turnover, given the observations of Kopin et al,³⁴ the potential for transcranial extraction of circulating MHPG to dramatically influence our results seems minimal.

Whole-Body Norepinephrine and Epinephrine Kinetics

After steady-state arterial plasma concentrations of ³H-norepinephrine and ³H-epinephrine had been reached, the overall release rate into plasma of endogenous norepinephrine and epinephrine were determined according to the well-described isotope dilution technique.^{24,26}

Cerebral Metabolism

The stoichiometry governing glucose oxidation indicates that equimolar amounts of oxygen are consumed for every mole of carbon dioxide produced,³⁵ hence the gas exchange ratio, or respiratory quotient, of the brain is 1. Deviations from unity indicate that substrates other than glucose are being used as energy sources.

The total oxygen content of the blood samples obtained was determined according to the following formula:

$$\text{Total O}_2 = (\text{Hb} \times \text{SO}_2 \times 1.34) + (0.003 \times \text{PO}_2),$$

where Hb, SO₂, and PO₂ are the measured hemoglobin concentration, oxygen saturation, and partial pressure of oxygen, respectively, 0.003 is the oxygen solubility coefficient, and 1.34 is the stoichiometric oxygen-binding capacity of the hemoglobin molecule (the Hufner number).

Whole-blood carbon dioxide content was calculated using the equation of Douglas et al³⁶:

$$\text{CO}_2 \text{ Content} = \text{Plasma CO}_2 \times (1 - [0.0289 \times \text{Hb}] / [3.352 - 0.456 \times \text{SO}_2] \times [8.142 - \text{pH}]),$$

where the plasma CO₂ content is estimated from the partial pressure of CO₂ (PCO₂), and the pH according to the Henderson-Hasselbach equation:

$$\text{Plasma CO}_2 = 2.226 \times \text{PCO}_2 (1 + 10^{\text{pH} - 6.0907}),$$

where 2.226 is the plasma CO₂ solubility coefficient and 6.0907 is the apparent equilibrium constant of the CO₂-bicarbonate system.³⁷

The cerebral respiratory quotient was determined by dividing the carbon dioxide produced by the oxygen consumed by the brain, and was calculated according to the following formula:

$$\text{Respiratory quotient} = (\text{Jugular CO}_2 \text{ Content} - \text{Arterial CO}_2 \text{ Content}) / (\text{Arterial O}_2 \text{ Content} - \text{Jugular O}_2 \text{ Content}).$$

STATISTICAL ANALYSIS

All results, unless otherwise specified, are expressed as means \pm SDs, and tests of significance were carried out using distribution-free nonparametric tests. Comparisons between groups were evaluated using the Wilcoxon test for unpaired observations. Evaluation of the effect of desipramine was evaluated using the Wilcoxon signed rank test for paired samples. Relationships between variables were evaluated with the Spearman rank correlation test. Significance levels greater than 5% were not considered to be significant.

orders. Earlier reports documenting similar cerebral norepinephrine and metabolite overflows in healthy subjects and in patients with autonomic failure, in whom there was existing evidence of almost complete postganglionic sympathetic denervation,¹⁶ provided the justification that the norepinephrine and metabolites measured emanate from central noradrenergic neurons and not from cerebrovascular sympathetic nerves.¹⁷ The inability of gan-

glionic blockade to reduce cerebral norepinephrine overflow underpins the concept of a central origin of the norepinephrine found in these studies.¹⁷ To our knowledge, this is the first report using such methods in patients with depressive illness with internal jugular venous concentration gradients, providing a window into the brain in depressive illness to investigate Schildkraut's catecholamine hypothesis of mood disorders.¹

Table 1. Clinical Data of Patients With Treatment-Refractory Nonbipolar Mood Disorders*

| Patient No./ Sex/Age, y | Age at Onset, y | DSM-IV Depression | DSM-IV Dysthymia | Melancholic Features | HDRS† | HDRS‡ | Previous Medication | No. of Days off Medication |
|-------------------------|-----------------|-------------------|------------------|----------------------|-------|-------|---------------------------|----------------------------|
| 1/M/62 | 44 | Yes | No | Yes | 28 | 28 | Citalopram | 32 |
| 2/M/41 | 30 | No | Yes | No | 14 | 14 | Fluoxetine | 23 |
| 3/M/44 | 41 | Yes | No | Yes | 33 | 15 | Nefazodone | 64 |
| 4/F/54 | 45 | Yes | No | Yes | 27 | 25 | Mirtazapine | 20 |
| 5/M/52 | 27 | Yes | No | No | 17 | 17 | Fluoxetine | 25 |
| 6/M/44 | 35 | Yes | No | No | 26 | 18 | Venlafaxine | 20 |
| 7/F/44 | 20 | Yes | No | Yes | 32 | 22 | Sertraline, mianserin | 20 |
| 8/M/44 | 13 | Yes | No | No | 22 | 22 | Moclobemide Amitriptyline | 20 |
| 9/M/41 | 26 | Yes | No | No | 18 | 17 | Venlafaxin | 20 |

*DSM-IV Depression indicates a DSM-IV diagnosis of major unipolar depression; DSM-IV Dysthymia, DSM-IV diagnosis of dysthymia.

†Seventeen-item Hamilton Depression Rating Scale (HDRS) scores for the worst week of the present depression episode, as extracted from the Schedule for Affective Disorders and Schizophrenia.^{18,19}

‡Hamilton Depression Rating Scale scores for the last week preceding investigation, of present depression episode, as extracted from the Schedule for Affective Disorders and Schizophrenia.^{18,19}

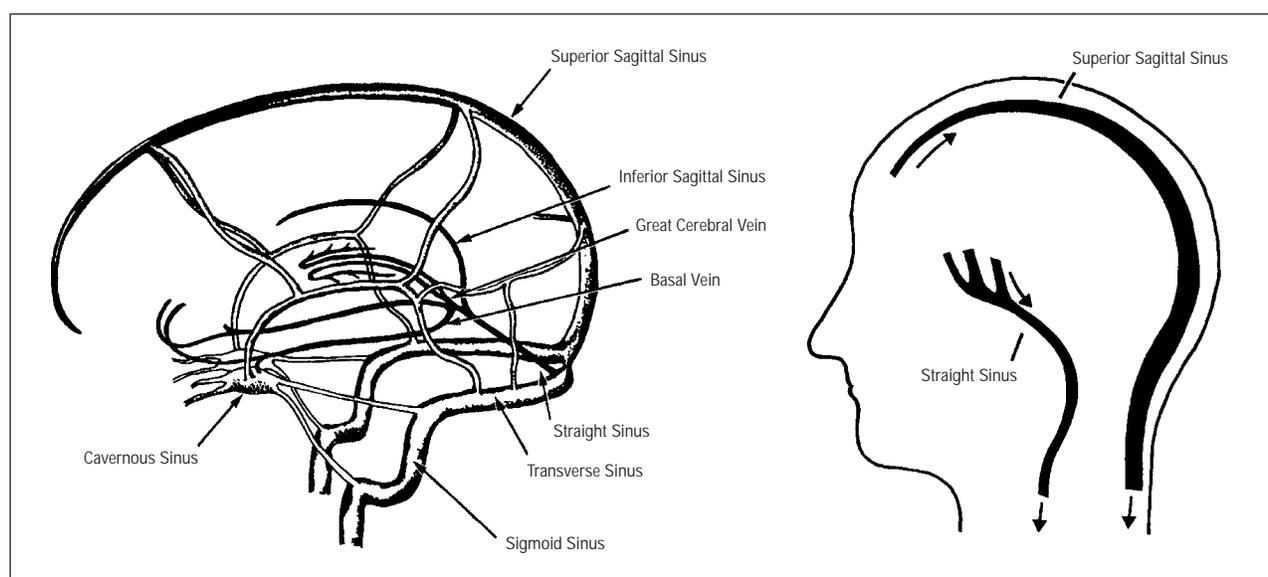


Figure 1. Left, Diagrammatic representation of the venous sinuses of the dura mater and their association with the cerebral veins. The superior sagittal sinus runs backwards across the falx cerebri and predominantly drains the cerebral hemispheres.²⁰ As the sinus nears the internal occipital protuberance, it deviates to one side or the other and forms the transverse sinus, which in turn becomes an internal jugular vein. Although this vessel contains the bulk of cortical venous effluent, it also contains blood derived from some subcortical areas via the cavernous sinus. Subcortical brain regions drain predominantly into the inferior sagittal and straight sinuses, which generally form the transverse sinus on the opposite side of that derived from the superior sagittal sinus. The inferior sagittal sinus receives a small amount of cortical venous effluent from the falx cerebri. Figure adaptation reprinted from Gray's Anatomy (Figure 6.121, page 743, 1995) by permission of the publisher Churchill Livingstone. Right, Schematic representation of the venous sinus drainage of the brain. The internal jugular vein receiving the superior sagittal sinus typically has a greater blood flow than the internal jugular vein receiving the inferior and straight sinuses.

RESULTS

CLINICAL CHARACTERISTICS

The clinical evaluation of the patients examined is summarized in Table 1. At the time of examination, 5 of the patients documented their degree of depression at a level approximating that experienced during their worst week of depressive illness.

SYSTEMIC NEUROCHEMICAL CONCENTRATIONS

Arterial plasma concentrations of norepinephrine, DHPG, MHPG, and 5-HIAA did not differ between the

patients with depressive illness and their healthy counterparts (**Table 2**). As Table 2 presents, the arterial plasma concentration of HVA was reduced in patients with depression and rates of total-body epinephrine and norepinephrine spillover into plasma were similar between groups.

INTERNAL JUGULAR CONCENTRATION GRADIENTS

Consistent with a reduction in central nervous system norepinephrine and dopamine turnover, the venoarterial norepinephrine, DHPG and MHPG, and HVA plasma concentration gradients across the brain were significantly reduced in the patients with depressive ill-

Table 2. Arterial Plasma Concentration of a Variety of Neurochemicals*

| Compound | Control Subjects (n = 19) | Patients With Depressive Illness (n = 9) |
|---|---------------------------|--|
| Norepinephrine | 1.5 ± 0.7 | 1.8 ± 1.1 |
| DHPG | 5.5 ± 1.0 | 6.3 ± 1.7 |
| MHPG | 15.5 ± 3.5 | 14.7 ± 4.1 |
| HVA | 47.4 ± 15.7 | 30.9 ± 13.6† |
| 5-HIAA | 51.0 ± 20.3 | 37.8 ± 9.8 |
| Cerebral ³ H-NE extraction, % arterial | 0.21 ± 0.15 | 0.06 ± 0.10† |
| Total body NE spillover, nmol/min | 3.7 ± 1.9 | 4.3 ± 2.4 |
| Total body EPI spillover, nmol/min | 0.8 ± 0.4 | 0.8 ± 0.9 |

*All values are presented as mean ± SD nmol/L, unless otherwise indicated. DHPG indicates dihydroxyphenylglycol; MHPG, 3-methoxy-4-hydroxyphenylglycol; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; ³H-NE, infused tritiated norepinephrine; NE, norepinephrine; and EPI, epinephrine.
†P < .05.

ness (**Figure 2**). The internal jugular venous increments of 5-HIAA did not differ between the 2 groups ($P = .5$). Data obtained from those patients who had previously been taking fluoxetine were not significantly different from those obtained from other patients. The internal jugular venous increment of HVA was positively correlated with the patients' past-week Hamilton Depression Rating Scale (HDRS) scores ($P = .02$, $r_s = 0.79$). No such relation existed between the patients' HDRS ratings and the internal jugular concentration gradients of norepinephrine and metabolites ($P = .57$) or 5-HIAA ($P = .79$). There was no direct association between the internal jugular concentration gradient of any of the compounds measured and age, sex, duration of illness, previous medication, or presence of melancholia.

CEREBRAL OXIDATIVE METABOLISM

Cerebral respiratory quotients in the patients with depressive illness were lower than those values obtained for the healthy subjects (**Figure 3**). At rest in these patients, there was no association between the brain's extraction of glucose and its extraction of oxygen ($P = .21$) or its production of carbon dioxide ($P = .21$).

ACUTE DESIPRAMINE ADMINISTRATION

Following intravenous desipramine administration in patients with depressive illness: (1) the combined internal jugular venous increments of norepinephrine, MHPG, and DHPG were increased from 0.66 ± 1.34 nmol/L to 2.67 ± 2.68 nmol/L ($P < .05$); (2) the reduced respiratory quotients were normalized (Figure 2; $P < .01$); and (3) the brain's extraction of glucose and its extraction of oxygen were positively associated ($P < .05$, $r_s = 0.62$). Desipramine did not significantly influence the arterial concentration of any of the compounds examined, the internal jugular venous overflow of HVA (3.1 ± 1.9 vs 3.6 ± 1.2 nmol/L), or 5-HIAA (4.8 ± 13.2 vs 7.8 ± 12.4 nmol/min). Arteriovenous glucose extraction was not influenced by

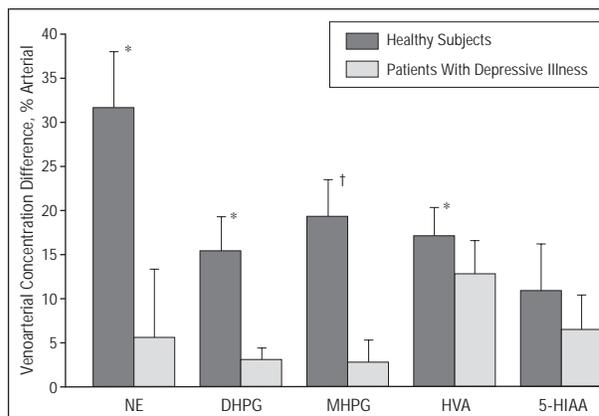


Figure 2. Internal jugular venous plasma concentration gradients of norepinephrine (NE) and its principal central nervous system-occurring metabolites, dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG), the dopamine metabolite homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in healthy subjects ($n = 19$) and in patients with unipolar depressive illness ($n = 9$). In 1 patient, internal jugular venous HVA overflow was not measured. Values shown are mean ± SE. Asterisk indicates $P < .05$; dagger, $P < .01$; values are significantly different from the corresponding values in healthy subjects.

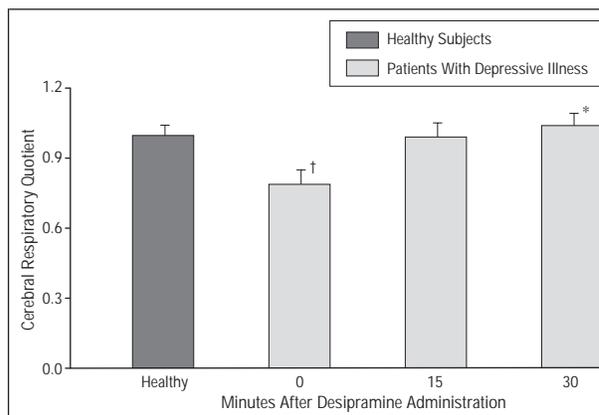


Figure 3. Indirect calorimetric assessment of cerebral respiratory quotients in healthy subjects ($n = 19$) and in patients with unipolar depressive illness ($n = 9$) at rest and in response to intravenous desipramine. Values shown are mean ± SE. Asterisk indicates $P < .01$; values are significantly different from the corresponding values in healthy subjects. Dagger indicates $P < .01$; significant effect of desipramine in normalizing the cerebral respiratory quotient in the subjects with depressive illness.

desipramine administration ($9.6\% \pm 3.6\%$ vs $10.1\% \pm 3.8\%$, $P = .56$).

COMMENT

The catecholamine hypothesis of mood disorders has gone through several modifications. The effectiveness of norepinephrine and serotonin uptake-blocking agents led to the identification of norepinephrine and serotonergic subtypes of the disorder.^{1,38,39} The knowledge that neuronal uptake blockade following antidepressant administration occurs rapidly but therapeutic effects may take from 2 to 6 weeks to occur⁴⁰ led to the formation of the alternative hypothesis that alterations in monoamine receptor sensitivity are crucial in the development of depressive illness.⁴¹ Another explanation, suggesting that

abnormalities in brain monoaminergic function arise secondary to stress-induced activation of the hypothalamic-pituitary-adrenal axis, has also been proposed.⁴² Interestingly, Esler et al⁸ and Veith et al⁹ have demonstrated elevated rates of norepinephrine spillover to plasma in patients with depression. While from our findings we cannot discount that alterations in monoaminergic receptor sensitivity or alternative routes of metabolism coexist with the deficiency in catecholamine overflow reported herein, many of the neuroendocrine alterations reported in patients with depressive illness, such as increased plasma cortisol levels, may arise as a consequence of reduced brain noradrenergic activity. The relative normality of rates of epinephrine secretion documented in our report does not support the idea that alterations in brain monoaminergic function arise as a consequence of activation of the hypothalamic-pituitary-sympathoadrenal axis in response to stress.

Our findings are somewhat paradoxical in nature. Desipramine, being a tricyclic antidepressant that blocks the neuronal reuptake of norepinephrine, is effective in increasing internal jugular norepinephrine and metabolites and restoring cerebral oxidative metabolism; yet, our estimation of central noradrenergic function was not related to the underlying clinical symptoms of patient depression. Moreover, the efficacy of specific serotonin uptake-blocking drugs provides persuasive evidence implicating serotonergic involvement in the development of depressive illnesses, yet the internal jugular venous 5-HIAA concentration gradient was not significantly diminished in our patient group. Cerebrospinal fluid 5-HIAA levels are normal in nonsuicidal depressed patients, but low in patients with a predisposition to violent suicide.⁴³ Given that none of our patients exhibited a history of suicide attempt or ideation, the apparent normality of brain serotonin in our patients may not be surprising. Alternatively, confounding influences of previous medications and inadequate drug washout cannot be unequivocally discounted.

From our observations, the role of dopamine in depressive illness is difficult to reconcile. As a group, internal jugular HVA concentration gradients are reduced while the "degree" of the patients' depression is positively correlated with our estimate of brain dopamine turnover. Interestingly, a meta-analysis of cerebrospinal fluid HVA levels demonstrates a consistent reduction in patients with depression.⁴⁴ This observation is consistent with evidence indicating that direct-acting dopaminergic agonists are effective antidepressants.⁴⁵ In our study, desipramine was without effect on internal jugular HVA levels. While the majority of brain dopamine is located in the nigrostriatal system, an area primarily concerned with motor control, the behavioral functions of the mesolimbic/mesocortical system make brain dopamine a likely candidate for involvement in depression. Although our methods are able to discriminate between cortical and subcortical dopaminergic responses to pharmacological challenges,⁴⁶ we are unable to differentiate between neuronal groups with similar fields of drainage.

The lack of a stoichiometric relationship between internal jugular venous oxygen and carbon dioxide and

glucose implies that the oxygen is being used for the oxidation of substances other than carbohydrates. Reduced cerebral metabolism, in line with an apparent diminution in brain monoaminergic activity, has been reported in patients with depressive illness.² Interestingly, indicators of brain noradrenergic function are negatively correlated to blood-brain barrier permeability.² The observation that defects in cerebral microcirculation in the tetrabenazine model of depression are associated with depletion of brain catecholamines,⁴⁷ coupled with the increased vulnerability of the blood-brain barrier to hypertensive insults following depletion of brain norepinephrine,⁴⁸ indicates that central noradrenergic neurons are important in the regulation of cerebral microcirculation.⁴⁹ It would seem that in patients with depressive illness, in whom we believe brain norepinephrine and dopamine turnover to be reduced, blood-brain barrier permeability may be increased. The consistency of cerebral glucose extraction prior to and following desipramine suggests that the carrier-mediated transport of glucose across the blood-brain barrier is not impaired. It would seem that the diminished cerebral respiratory quotients in our patients arise, not as a consequence of a defect in cerebral glucose metabolism per se, but as a result of the diffusion and metabolism of other energy substrates across the blood-brain barrier. The clinical importance of this is uncertain given that glucose metabolism is normalized immediately following antidepressant administration and therapeutic effects may take from 2 to 6 weeks to occur.⁴⁰

This was an invasive catheter study performed in patients and healthy volunteers, and for this reason some ethical considerations should be addressed. The 3 central ethical issues in relation to clinical research are generally: (1) the quality of the research, (2) the potential for harm to an individual intrinsic to the research, and (3) the degree of safeguarding the autonomy of the subjects participating in the experiments.⁵⁰

In this study we investigated a long-standing hypothesis of considerable clinical significance using well-developed methods to provide information concerning central nervous system abnormalities in depressive illness. Throughout the process of recruitment, patients were assured that their participation was voluntary and that the research was designed to achieve a greater understanding of depressive illness in general rather than providing results of specific relevance to their immediate treatment. Patients with depressive illness are assumed competent to give consent. The process of consent, for which an explicit patient information sheet was implicit, conformed to the standard expected in preserving the autonomy of the patients.

In accordance with the principal tenet of the Schildkraut hypothesis that "some, if not all, depressions are associated with an absolute or relative decrease in catecholamines, particularly norepinephrine, available at central adrenergic receptor sites,"¹ we have demonstrated the existence of a substantial reduction in the internal jugular venoarterial concentration gradients of norepinephrine and dopamine metabolites in patients with nonbipolar depressive illness. Moreover, the brains of these patients use an energy source other than glucose, a situ-

ation that is normalized following the acute blockade of the norepinephrine transporter with the tricyclic antidepressant, desipramine.

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