Psychiatry Research, 52:115-123
Elsevier

Relationship Between Alpha$_2$-Adrenergic Function and Suicidal Behavior in Depressed Patients

William Pitchot, Marc Ansseau, Antonio Gonzalez Moreno, Jacques Wauthy, Michel Hansenne, and Remy von Frenckell

Received June 3, 1992; revised version received June 3, 1993; accepted July 23, 1993.

Abstract. The current main neurochemical theories of the biological correlates of suicidal behavior involve serotonergic and, to a lesser extent, dopaminergic systems. Few data are available about the possible implication of the noradrenergic function. In the present study, we assessed the growth hormone response to clonidine, a selective α_2-adrenergic agonist, in 15 *DSM-III-R* major depressive inpatients with a history of suicide attempts, compared with 15 age- and gender-matched major depressive inpatients without a history of suicidal behavior. Mean ($\pm$ SD) growth hormone peak responses to clonidine were significantly lower in the group of suicide attempters than in the control group: 2.93 ± 3.01 ng/ml vs. 8.28 ± 8.15 ng/ml. Therefore, these results suggest that a blunted growth hormone response to clonidine could be a biological correlate of suicidal behavior.

Key Words. Affective disorder, growth hormone, clonidine, norepinephrine.

The prevailing neurochemical theory about biological correlates of suicidal behavior focuses on the serotonergic system. In 1976, Åsberg et al. found a bimodal distribution of cerebrospinal fluid (CSF) concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in depression (Åsberg et al., 1976*a*). They showed that patients who attempted suicide before being hospitalized had low CSF 5-HIAA levels compared with those without a history of suicide attempt (Åsberg et al., 1976*b*). Several studies in different diagnostic categories confirmed that patients who attempted suicide had lower CSF 5-HIAA levels than control subjects (Brown et al., 1979, 1982; Ågren, 1980; Träskman et al., 1981; van Praag, 1982, 1983; Banki and Arató, 1983; Ninan et al., 1984). The role of serotonin in the biology of suicidality was also assessed in post-mortem (Mann et al., 1986*a*) and platelet studies (Meltzer and Arora, 1986) with controversial results.

A dopamine dysfunction could also be related to suicidal behavior. Indeed, some studies reported low CSF levels of the dopamine metabolite homovanillic acid in depressed patients with a history of suicide attempt (Ågren, 1980, 1983; Träskman et al., 1981; Montgomery and Montgomery, 1982; Roy et al., 1986). Recently, we showed

William Pitchot, M.D., is Resident; Marc Ansseau, M.D., Ph.D., is Head; Antonio Gonzalez Moreno, M.D., is Resident; Jacques Wauthy, B.Sc., and Michel Hansenne, B.Sc., are Psychologists; and Remy von Frenckell, Ph.D., is Senior Statistician, Psychiatric Unit, University Hospital Center of Liège, Belgium. (Reprint requests to Dr. W. Pitchot, Service de Psychiatrie, Centre Hospitalier Universitaire de Liège, B-4000 Liège, Belgium.)

Elsevier Science Ireland Ltd.

that patients with a history of suicidal behavior exhibited a significantly lower growth hormone (GH) response to apomorphine, a selective dopaminergic agonist, than patients who had never attempted suicide (Pitchot et al., 1992). This finding suggested that a hyposensitivity of dopaminergic receptors could be related to suicidal behavior.

Few data are available about the implication of the noradrenergic system in suicidal patients. In 1976, Beskow et al. showed a decrease of norepinephrine levels in the putamen of suicide victims. In post-mortem studies, β-adrenergic receptor binding has been found significantly increased in the frontal cortex of suicide victims compared with controls (Zanko and Biegon, 1983; Mann et al., 1986*b*). Secunda et al. (1986) showed smaller urinary outputs of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and a lower plasma concentration of MHPG in suicide attempters compared with patients without a history of suicidal behavior. CSF studies have also provided additional but inconsistent data for the noradrenergic hypothesis of suicidal behavior. Brown et al. (1979) found higher levels of CSF MHPG in personality disordered patients with a history of suicide attempts than in control subjects. Ågren (1980) reported a negative correlation between measures of suicidal tendencies and CSF MHPG levels in depressed patients. However, Roy et al. (1989), who studied CSF, urinary, and plasma indices of noradrenergic function, did not find any relationship between norepinephrine and suicidal behavior.

In this context, the aim of the present study was to assess noradrenergic function in depressed suicide attempters by measuring the GH response to an intravenous clonidine challenge. Clonidine exhibits a highly specific α_2-adrenergic agonistic activity and stimulates GH secretion through postsynaptic α_2-adrenergic receptors in the hypothalamus (Lal and Martin, 1980; Siever et al., 1982). This clonidine-induced GH response appears to be blunted among major depressive patients (Matussek et al., 1980; Checkley et al, 1981, 1984; Charney et al., 1982; Siever et al., 1982; Siever and Uhde, 1984; Boyer et al., 1986; Ansseau et al., 1988), supporting an α_2-adrenergic receptor disturbance in major depressive disorders. Here, we postulated that blunted GH responses to clonidine might be related to suicidal behavior in depressed patients.

Methods

Subjects. The study was performed in 15 *DSM-III-R* major depressive inpatients with a history of suicide attempts (American Psychiatric Association, 1987) during the current episode. The patients were consecutive admissions to the Psychiatric Unit of the University Hospital of Liège, Belgium. Most of the patients (13/15) have been included in another study (Pitchot et al., 1992). Table 1 presents individual characteristics of patients 1-15. The sample comprised nine male and six female patients with a mean age of 39.2 (SD = 9.7). These patients were individually matched for gender, age (within 3 years) and, in the case of women, menopausal status to 15 major depressive inpatients without a history of suicidal behavior (Table 1: patients 16-30). The two groups did not differ in mean age or weight. All patients had a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960) at the end of a drug-free period of at least 2 weeks. Moreover, there was no difference in washout periods between the two groups.

Past history of suicide attempt was based on interviews with the patients and their family members. Suicide attempts were classified as violent (hanging, drowning, deep cuts, and

shooting) or nonviolent (drug overdoses and superficial wrist cuts). All patients were free of medical illness as evidenced by history, medical examination, electrocardiogram, chest x-ray, electroencephalogram, and routine laboratory tests. The clonidine test was performed between days 3 and 12 of the menstrual cycle in premenopausal women (Tulandi et al., 1987). Patients with a basal systolic blood pressure $<$ 100 mmHg were excluded from the study. Moreover, to be included, patients had to have a basal (t_0) GH level $<$ 5 ng/ml before the pharmacological challenge (Ansseau et al., 1984). The exclusion of subjects with basal GH values $>$ 5 ng/ml was recommended by Laakmann (1990) who demonstrated that "prestimulator" healthy volunteers responded significantly less to a noradrenergic challenge than healthy volunteers with low basal values. Finally, the protocol was approved by the Ethical Committee of the University of Liège Medical School, and all patients were fully informed of the study and gave their consent.

Neuroendocrine Test Procedure. The clonidine test was performed in all subjects at bedrest after an overnight fast. At 7 a.m., an indwelling catheter was inserted in a forearm vein. Blood samples of 10 ml were collected at -20, 0, 20, 40, 60, and 120 minutes after injection at 8 a.m. of clonidine, 0.15 mg diluted in saline to obtain 20 cc intravenously in 10 minutes.

GH was measured with a double antibody radioimmunoassay (Franchimont, 1968), with intra-assay and interassay coefficients of variation of, respectively, 13.3 ± 4.7% and 14.8 ± 9.6% and a detection limit of 0.2 ng/ml.

Data Analysis. GH responses to clonidine were assessed by GH peak values following injection and by the area under the curve (AUC) between t_0 and t_{120} minutes. Analyses were performed using absolute GH values as well as differences related to basal (t_0) levels (relative values). Since the correlations between absolute and relative values were very high ($r > 0.98$), only absolute values are reported here. The responses of patients with and without a history of suicide attempt as well as violent and nonviolent suicide attempters were compared by analysis of covariance (ANCOVA) for age and weight.

Results

There was a significantly weaker GH response to the clonidine test in the group of suicide attempters than in the group without a history of suicidal behavior for the GH peak responses (mean ± SD = 2.93 ± 3.01 ng/ml vs. 8.28 ± 8.15 ng/ml; $F = 3.63$; $df = 3, 26$; $p = 0.026$) and for the log of AUC values ($F = 2.0$; $df = 2, 28$; $p < 0.05$). GH responses to clonidine did not differ significantly between melancholic and nonmelancholic depressed patients ($F = 1.22$; $df = 3, 26$; $p = 0.32$). There was no correlation betwen mean GH responses and scores on the Hamilton Rating Scale for Depression ($r = -0.004$, $p = 0.98$).

Mean GH responses to clonidine did not differ between nonviolent (mean ± SD = 3.4 ± 3.08 ng/ml) and violent (mean ± SD = 2.52 ± 3.10 ng/ml) attempters ($F = 0.66$; $df = 3, 11$; $p = 0.59$). Moreover, the time between the suicide attempt and the neuroendocrine investigation was not correlated with GH responses ($r = -0.41$, $p = 0.12$).

Discussion

The results of the present study suggest an involvement of the noradrenergic system, particularly α_2-adrenergic function, in the expression of suicidal behavior. Indeed, suicide attempters exhibited smaller GH responses to clonidine than patients without a history of suicide attempts. Thus, a hyposensitivity of α_2-adrenergic receptors

Table 1. Individual characteristics of the sample and neuroendocrine results

Patient	Sex	Age (yr)	Weight (kg)	HRSD	Tsa	Nsa	Diagnosis	History of suicide attempt	Clonidine GH peak: ng/ml
1	F	23	62	20	3	4	MDD, nonmelancholic, UP	Drug overdose	8.2
2	M	26	64	25	3.5	2	MDD, nonmelancholic, UP	Drug overdose	1.0
3	M	27	83	29	3	3	MDD, nonmelancholic, UP	Drug overdose	0.7
4	F	33	73	18	6	2	MDD, nonmelancholic, UP	Drug overdose	1.7
5	M	34	76	25	3	1	MDD, nonmelancholic, UP	Hanging	3.0
6	M	36	66	38	7	1	MDD, melancholic, UP	Defenestration	0.3
7	M	38	60	24	3	2	MDD, melancholic, UP	Hanging	6.5
8	M	41	70	35	150	1	MDD, melancholic, UP	Hanging	0.1
9	M	42	79	18	4	1	MDD, nonmelancholic, UP	Drowning	8.0
10	F	44	69	25	3	3	MDD, melancholic, BP	Drug overdose	2.1
11	F	46	63	35	24	1	MDD, melancholic, UP	Drug overdose	7.4
12	M	49	83	33	100	1	MDD, nonmelancholic, UP	Shooting	1.7
13	M	55	87	20	48	1	MDD, nonmelancholic, UP	Hanging	0.3
14	F	39	70	18	8	1	MDD, nonmelancholic, UP	Drug overdose	2.7
15	F	55	71	25	100	1	MDD, melancholic, UP	Shooting	0.3
Mean	9M,6F	39.2	71.7	25.8	31.0				2.93
SD		9.7	8.3	6.7	47.2				3.01

Patient	Sex	Age (yr)	Weight (kg)	HRSD	Tsa	Nsa	Diagnosis	History of suicide attempt	Clonidine GM peak: ng/ml
16	F	26	67	18	—	—	MDD, nonmelancholic, UP	—	16.1
17	M	29	70	26	—	—	MDD, melancholic, UP	—	27.7
18	M	29	70	26	—	—	MDD, melancholic, UP	—	1.0
19	F	36	49	35	—	—	MDD, nonmelancholic, UP	—	12.8
20	M	37	87	29	—	—	MDD, melancholic, BP	—	0.8
21	M	34	84	28	—	—	MDD, nonmelancholic, UP	—	2.5
22	M	36	74	30	—	—	MDD, nonmelancholic, UP	—	0.5
23	M	41	88	23	—	—	MDD, nonmelancholic, UP	—	0.2
24	M	45	103	18	—	—	MDD, nonmelancholic, UP	—	3.4
25	F	42	52	21	—	—	MDD, nonmelancholic, UP	—	12.7
26	F	44	52	25	—	—	MDD, melancholic, UP	—	2.8
27	M	48	72	24	—	—	MDD, nonmelancholic, UP	—	6.9
28	M	57	72	27	—	—	MDD, nonmelancholic, UP	—	8.3
29	F	36	74	33	—	—	MDD, nonmelancholic, UP	—	19.6
30	F	55	75	35	—	—	MDD, melancholic, BP	—	8.9
Mean	9M,6F	39.6	72.6	26.5					8.28
SD		9.07	14.5	5.4					8.15

Note. MDD = major depressive disorder. UP = unipolar. BP = bipolar. Tsa = time in weeks between the suicide attempt and the investigation. Nsa = number of suicide attempts. HRSD = Hamilton Rating Scale for Depression. GH = growth hormone. M = male. F = female.

could be a determinant of suicidal behavior in depressed patients. Moreover, the lack of correlation between GH responses and the time between suicide attempt and neuroendocrine investigation suggests that the clonidine test might be a "trait marker" for suicidal behavior. This interpretation is consistent with previous reports that considered a blunted GH response to clonidine as an indicator of higher vulnerability to endogenous depressive illness (Checkley et al., 1984; Siever and Uhde, 1984; Hoehe et al., 1986; Siever et al., 1986; Ansseau et al., 1987; Mitchell et al., 1988). However, longitudinal studies are needed to determine if a persistent hyposensitivity of α_2-adrenergic receptors might be a predictor of suicide.

Our results are in agreement with previous studies showing a trend for a decrease of noradrenergic activity in depressed patients with a history of suicidal behavior. In 1982, Ostroff et al. found a lower 24-hour urinary norepinephrine-to-epinephrine ratio in three depressive patients with a history of severe suicide attempts compared with depressed control subjects without a history of suicidal behavior. Secunda et al. (1986) reported low urinary and plasma MHPG measures in suicide attempters compared with control subjects. CSF MHPG levels exhibited a similar trend only in bipolar patients (Secunda et al., 1986). Ågren (1980) showed a negative correlation between CSF MHPG concentrations and measures of suicidality in depressed patients. However, these results were not confirmed in a recent study by Roy et al. (1989) who did not find any relationship betweeen CSF, urinary, and plasma indices of noradrenergic activity and history of suicide attempt. In fact, these studies measured a generalized noradrenergic underactivity. In the present study, we specifically assessed postsynaptic α_2-adrenergic receptor sensitivity in the hypothalamic-pituitary axis.

No significant difference in GH responses was found between violent and nonviolent suicide attempters suggesting that disturbances in the sensitivity of α_2-adrenergic receptors are not related to impulsive autoaggression. This observation is somewhat at variance with a recent report by Coccaro et al. (1992), who found a positive correlation between GH responses to clonidine and the Buss-Durkee Hostility Inventory "irritability" subscale, but not the "assault" subscale, in personality disordered patients and healthy volunteers. Here, in depressed patients, an α_2-adrenergic receptor hyposensitivity seems more related to suicidality as such than to a dysfunction in the regulation of aggression. However, our sample size is too small to exclude definitively a role for the noradrenergic system in the type of suicide attempt.

A pitfall in this study is that the 2-week drug-free washout period may have been insufficient. Indeed, several reports have suggested that tricyclic antidepressants may impair the GH response to clonidine for periods longer than 3 weeks following their discontinuation (Corn et al., 1984; Schittecatte et al., 1989). Moreover, the difference between depressed patients with or without a history of suicidal behavior is rather weak, and our results should obviously be confirmed in further studies with larger numbers of patients. It would also be interesting to investigate the GH responses to clonidine in nondepressed suicidal patients.

In conclusion, this study suggests that a blunted GH response to clonidine could serve as a biological marker of suicidal behavior. This hypothesis requires confirmation and further development.

References

Ågren, H. Symptom patterns in unipolar and bipolar depression correlating with monoamine metabolites in the cerebrospinal fluid: II. Suicide. *Psychiatry Research,* 3:225-236, 1980.

Ågren, H. Life at risk: Markers of suicidality in depression. *Psychiatric Developments,* 1:87-104, 1983.

American Psychiatric Association. *DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed., revised. Washington, DC: American Psychiatric Press, 1987.

Ansseau, M.; Scheyvaerts, M.; Doumont, A.; Poirrier, R.; Legros, J.J.; and Franck, G. Concurrent use of REM latency, dexamethasone suppression, clonidine, and apomorphine tests as biological markers of endogenous depression: A pilot study. *Psychiatry Research,* 12:261-272, 1984.

Ansseau, M.; von Frenckell, R.; Cerfontaine, J.L.; Papart, P.; Franck, G.; Timsit-Berthier, M.; Geenen, V.; and Legros, J.J. Neuroendocrine evaluation of catecholaminergic neurotransmission in mania. *Psychiatry Research,* 22:193-206, 1987.

Ansseau, M.; von Frenckell, R.; Cerfontaine, J.L.; Papart, P.; Franck, G.; Timsit-Berthier, M.; Geenen, V.; and Legros, J.J. Blunted response of growth hormone to clonidine and apomorphine in endogenous depression. *British Journal of Psychiatry,* 153:65-71, 1988.

Åsberg, M.; Thorén, P.; Träskman, L.; Bertilsson, L.; and Ringberger, V. Serotonin depression: A biochemical subgroup within the affective disorders. *Science,* 191:478-480, 1976*a*.

Åsberg, M.; Träskman, L.; and Thorén, P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor. *Archives of General Psychiatry,* 33:1193-1197, 1976*b*.

Banki, C.M., and Arató, M. Amine metabolites and neuroendocrine response related to depression and suicide. *Journal of Affective Disorders,* 5:223-232, 1983.

Beskow, J.; Gottfries, C.; Roos, B.; and Winblåd, B. Determination of monoamine and monoamine metabolites in the human brain: Post-mortem studies in a group of suicides and in a control group. *Acta Psychiatrica Scandinavica,* 53:7-20, 1976.

Boyer, P.; Davila, M.; Schaub, C.; and Nassiet, J. Growth hormone response to clonidine stimulation in depressive states: Part I. *Psychiatrie et Psychobiologie,* 1:189-195, 1986.

Brown, G.L.; Ebert, M.H.; Goyer, P.F.; Jimerson, D.C.; Klein, W.J.; Bunney, W.E.; and Goodwin, F.K. Aggression, suicide, and serotonin: Relationship to CSF amine metabolites. *American Journal of Psychiatry,* 139:741-746, 1982.

Brown, G.L.; Goodwin, F.K.; Ballenger, J.L.; Goyer, P.F.; and Major L.F. Aggression in humans: Correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research,* 1:131-139, 1979.

Charney, D.S.; Heninger, G.R.; Sternberg, D.E.; Hafstad, K.M.; Giddings, S.; and Landis, D.H. Adrenergic receptor sensitivity in depression: Effects of clonidine in depressed patients and healthy subjects. *Archives of General Psychiatry,* 39:290-294, 1982.

Checkley, S.A.; Glass, I.B.; Thompson, C.; Corn, T.; and Robinson, P. The GH response to clonidine in endogenous as compared with reactive depression. *Psychological Medicine,* 14:773-779, 1984.

Checkley, S.A.; Slade, A.P.; and Shur, E. Growth hormone and other responses to clonidine in patients with endogenous depression. *British Journal of Psychiatry,* 138:51-55, 1981.

Coccaro, E.F.; Lawrence, T.; Trestman, R.; Gabriel, S.; Klar, H.M.; and Siever, L.J. Growth hormone responses to intravenous clonidine challenge correlate with behavioral irritability in psychiatric patients and healthy volunteers. *Psychiatry Research,* 39:129-139, 1991.

Corn, T.H.; Thompson, C.; and Checkley, S.A. Effects of desipramine treatment upon central adrenoreceptor function in normal subjects. *British Journal of Psychiatry,* 145:139-145, 1984.

Franchimont, P. Le dosage radioimmunologique de l'hormone de croissance humaine. *Cahiers Médicaux Lyonnais,* 44:887-898, 1968.

Hamilton, M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry,* 23:56-62, 1960.

Hoehe, M.; Valido, G.; and Matussek, N. Growth hormone response to clonidine in endogenous depressive patients: Evidence for a trait marker in depression. In: Shagass, C.; Josiassen, R.C.; Bridger, W.H.; Weiss, K.S.; Stoff, D.; and Simpson, G.M., eds. *Biological Psychiatry 1985.* New York: Elsevier, 1986. p. 862.

Laakmann, G. *Psychopharmacoendocrinology and Depression Research.* Berlin: Springer-Verlag, 1990.

Lal, S., and Martin, J.B. Neuroanatomy and neuropharmacological regulation of neuroendocrine function. In: van Praag, H.M.; Lader, M.H.; Rafaelsen, O.J.; and Sachar, E.J., eds. *Handbook of Biological Psychiatry: Part III. Brain Mechanisms and Abnormal Behavior. Genetics and Neuroendocrinology.* New York: Marcel Dekker, 1980.

Mann, J.J.; McBride, P.A.; and Stanley, M. Post-mortem monoamine receptor and enzyme studies in suicide. *Annals of the New York Academy of Sciences,* 487:114-121, 1986*a*.

Mann, J.J.; Stanley, M.; Mc Bride, A.; and McEwen, B. Increased serotonin-2 and beta-adrenergic receptor binding in the frontal cortices of suicide victims. *Archives of General Psychiatry,* 43:984-995, 1986*b*.

Matussek, N.; Ackenheil, M.; Hippius, H.; Müller, F.; Schröder, H.T.; Schultes, H.; and Wasilewski, B. Effect of clonidine on growth hormone release in psychiatric patients and controls. *Psychiatry Research,* 2:25-36, 1980.

Meltzer, H.Y., and Arora, R.C. Platelet markers of suicidality. *Annals of the New York Academy of Sciences,* 487:271-280, 1986.

Mitchell, P.B.; Bearn, J.A.; Corn, T.H.; and Checkley, S.A. Growth hormone response to clonidine after recovery in patients with endogenous depression. *British Journal of Psychiatry,* 152:34-38, 1988.

Montgomery, S.A., and Montogomery, D. Pharmacological prevention of suicidal behavior. *Journal of Affective Disorders,* 4:291-298, 1982.

Ninan, P.T.; van Kammen, D.P.; Scheinin, M.; Linnoila, M.; Bunney, W.E., Jr.; and Goodwin, F.K. CSF 5-hydroxyindoleacetic acid levels in suicidal schizophrenic patients. *American Journal of Psychiatry,* 141:566-569, 1984.

Ostroff, R.; Giller, E.; Bonese, K.; Ebersole, E.; Harkness, L.; and Mason, J. Neuroendocrine risk factors of suicidal behavior. *American Journal of Psychiatry,* 139:1323-1325, 1982.

Pitchot, W.; Hansenne, M.; Gonzalez Moreno, A.; and Ansseau, M. Suicidal behavior and growth hormone response to apomorphine test. *Biological Psychiatry,* 31:1213-1219, 1992.

Roy, A.; Ågren, A.; Pickar, D.; Linnoila, M.; Doran, A.; Cutler, N.; and Paul, S. Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: Relationship to suicidal behavior and dexamethasone nonsuppression. *American Journal of Psychiatry,* 143:1539-1545, 1986.

Roy, A.; Pickar, D.; De Jong, J.; Karoum, F.; and Linnoila, M. Suicidal behavior in depression: Relationship to noradrenergic function. *Biological Psychiatry,* 25:341-350, 1989.

Schittecatte, M.; Charles, G.; Machowski, R.; and Wilmotte, J. Tricyclic wash-out and growth hormone response to clonidine. *British Journal of Psychiatry,* 154:858-863, 1989.

Secunda, S.; Cross, C.; Koslow, S.; Katz, M.; Kocsis, J.; Maas, J.; and Landis, H. Biochemistry and suicidal behavior in depressed patients. *Biological Psychiatry,* 21:756-767, 1986.

Siever, L.J.; Coccaro, E.F.; Adan, F.; Benjamin, E.; and Davis, K.L The growth hormone response to clonidine in acute and remitted affective disorder patients. In: Shagass, C.; Josiassen, R.C.; Bridger, W.H.; Weiss, K.S.; Stoff, D.; and Simpson, G.M., eds. *Biological Psychiatry 1985.* New York: Elsevier, 1986. p. 791.

Siever, L.J., and Uhde, T.W. New studies and perspectives on the noradrenergic receptor system in depression: Effects of the alpha-2-adrenergic agonist clonidine. *Biological Psychiatry,* 19:131-156, 1984.

Siever, L.J.; Uhde, T.W.; Silberman, E.K.; Jimerson, D.C.; Aloi, J.A.; Post, R.M.; and Murphy, D.L. Growth hormone response to clonidine as a probe of noradrenergic receptor responsiveness in affective disorder patients and controls. *Psychiatry Research,* 6:171-183, 1982.

Träskman, L.; Åsberg, M.; Bertilsson, L.; and Sjöstrand, L. Monoamine metabolites in CSF and suicidal behavior. *Archives of General Psychiatry,* 38:631-636, 1981.

Tulandi, T.; Lal, S.; and Guyda, H. Effect of estrogen on the growth hormone response to the alpha-adrenergic agonist clonidine in women with menopausal flushing. *Journal of Clinical Endocrinology and Metabolism,* 65:6-10, 1987.

van Praag, H.M. Depression, suicide and metabolism of serotonin in the brain. *Journal of Affective Disorders,* 4:275-290, 1982.

van Praag, H.M. CSF 5-HIAA and suicide in non-depressed schizophrenics. (Letter) *Lancet,* II:977-978, 1983.

Zanko, M., and Biegon, A. Increased beta-adrenergic receptor binding in human frontal cortex of suicide victims. *Abstracts of the 13th Annual Meeting of the Society for Neuroscience,* Boston, MA. Abstract 210.5, 1983.