OXFORD

International Journal of Neuropsychopharmacology, 2014, 1–6

doi:10.1093/ijnp/pyu023
Brief Report

BRIEF REPORT

Cerebrospinal Fluid Neuropeptide Y Levels in Major Depression and Reported Childhood Trauma

Laili Soleimani, MD; Maria A. Oquendo, MD, PhD; Gregory M. Sullivan, MD; Aleksander A. Mathé, MD; J. John Mann, MD

Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York (Dr Soleimani); Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute (Drs Oquendo, Sullivan, and Mann); Department of 3Psychiatry, Columbia University, New York (Drs Oquendo, Sullivan, and Mann); Department of Radiology, Columbia University, New York (Dr Mann); Division of Psychiatry, Karolinska Institute, Stockholm, Sweden (Dr Mathé).

Correspondence: J. John Mann, MD, New York State Psychiatric Institute, Box 42, 1051 Riverside Drive, New York NY 10032 (jjm@columbia.edu).

Abstract

Background: Neuropeptide Y (NPY) may enhance resilience to chronic stress. Low brain NPY reported in major depression may normalize in response to antidepressants.
Methods: In this study, we examined the relationship of reported childhood trauma to cerebrospinal fluid (CSF) NPY–like immunoreactivity (NPY-LI) in 61 medication-free major depressive disorder (MDD) patients and 20 matched healthy volunteers.
Results: Higher CSF NPY-LI was found in MDD compared to the healthy volunteer group ($p = 0.01$). A positive correlation of CSF NPY-LI with more adverse childhood trauma ($p = 0.001$) may be indicative of an intact but insufficient NPY-related stress response.
Conclusions: We hypothesize that differences in published results may be explained by the existence of two groups of MDD in terms of CSF NPY levels: MDD with low CSF NPY prior to stress or in response to stress, and those with robust NPY responses to stress. Future studies should confirm the two groups and seek the molecular mechanism for their differences.

Keywords: childhood trauma, CSF, major depression, neuropeptide Y

Introduction

Neuropeptide Y (NPY), a 36–amino acid peptide member of the pancreatic polypeptide family, is abundant in brain regions, including the amygdala and hippocampus, as a peptide neurotransmitter (Heilig, 2004).

NPY is associated with stress response and regulation. Low brain NPY levels are reported in pre-clinical models (Jimenez Vasquez et al., 2000, 2001), including animal models of posttraumatic stress disorder (PTSD; Cohen et al., 2012)), and some clinical studies of cerebrospinal fluid (CSF) NPY in depression and anxiety (Table 1). Conversely, studies find higher NPY brain levels—most consistently in the prefrontal cortex—in response to antidepressants and associated with resilience against stress (Wu et al., 2011). However, findings concerning the CSF NPY levels and clinical factors are inconsistent across studies. Because CSF and plasma NPY are weakly correlated (Baker et al., 2013), we have focused our summary in Table 1 on CSF studies.

Risk of major depression in adulthood is affected by genetic factors (Collier et al., 1996), childhood adversity (Wilkinson and Goodyer, 2011), and their interaction (Cervilla et al., 2007). Many studies of NPY in major depression do not consider the potential

Received: February 2, 2014; **Revised:** May 16, 2014; **Accepted:** June 5, 2014

Table 1. Summary of Clinical Studies Measuring CSF NPY-LI.

Author	Subjects	Methods (Samples, Techniques)	Results
Berrettini et al., 1987	MDD and bipolar, drug free: n = 38 Chronic schizophrenia, drug free: n = 20Chronic schizophrenia, medicated: n = 15Healthy volunteers: n = 33	CSF (NPY-LI) at baseline Schizophrenics hadrepeated CSF after 1 month of randomized fluphenazine (24 mg/d) txHigh pressure liquid chromatography	CSF NPY-LI: MDD = Medicated schizophrenia =Drug free schizophrenia = healthy volunteers
Widerlov et al., 1988	MDD, baseline, drug free: n = 33 / post tx (TCA. MAOI): n = 10Schizophrenia,baseline, drug free: n = 35 / post tx: n = 16Healthy volunteers: n = 22	CSF (NPY-LI) at baseline and after tx RIA	CSF NPY-LI: MDD<healthy volunteers or Schizophrenia No effect of tx in depression or schizophrenia
Traskman-Bendz et al., 1992	Suicide attempters, drug free:MDD: n=16Non-MDD: n=28	CSF (NPY-LI) RIA	CSF NPY-LI: MDD = Non-MDD
Heilig, 2004	MDD- TRD, drug free: n = 51 Healthy volunteers: n = 27	CSF (NPY-LI) CompetitiveRIA	CSF NPY-LI: MDD-TRD < healthy volunteers
Nikisch et al., 2005	MDD, hospitalized, drug free: n = 21	CSF (NPY-LI) at baseline and after 4 w citalopram tx RIA	CSF NPY-LI: Citalopramtx→↑NPY-LI and ↓CRH-LI
Hou et al., 2006	MDD-severe, drug free: n = 40 Healthy volunteers: n = 40	CSF (NPY-LI) ELISA	CSF NPY-LI: MDD=healthy volunteers 1st episode MDD < recurrent MDD
Nikisch and Mathe, 2008	MDD-TRD, drug free: n = 6	CSF (NPY- LI) at baseline and after 6 ECT tx RIA	CSF NPY-LI: ECT- tx→ ↑NPY-LI and ↓ CRH-LI
Sah et al., 2009	Chronic PTSD, Males, drug free: n = 10Healthy volunteers, Male: n = 13	CSF (NPY- LI) Competitive RIA	CSF NPY-LI: PTSD < healthy volunteers
Martinez et al., 2012	MDD-moderate, drug free: n = 18Healthy volunteers: n = 25	CSF (NPY-LI) at baseline and after 8 w tx ELISA	Baseline CSF NPY: MDD > healthy volunteers No effect of tx on NPY-LI
Nikisch et al., 2012	Schizophrenia: n = 22	CSF (NPY-LI and CRH-LI) at baseline and after 4 w quetiapine tx (600 mg/d) RIA	Quetiapine→ ↑NPY- LI and ↓CRH-LI and strongly correlated to the decrease in depression and anxiety PANSS items

CRH-LI, CRH-like immunoreactivity; d, day; ECT, electroconvulsive therapy; ELISA, enzyme-linked immunosorbent assay; MAOI, monoamine oxidase inhibitors; PANSS, positive and negative syndrome scale; RIA, radioimmunoassay; TCA, tricyclic antidepressants; TRD, treatment resistant depression; Tx, treatment; W, week.

role of childhood trauma on NPY levels (see Table 1 for review). Since major depression itself can be a severe stressor, NPY levels could either be increased as a result of a homeostatic response or have low levels, conferring lower resilience and increasing the risk of depression in the face of later adulthood stress.

The objective of this study was to test these two alternative models and identify the predominant model by examining CSF NPY–like immunoreactivity (NPY-LI) levels in drug-free, currently-depressed subjects with a major depressive disorder as compared to healthy volunteers, and to investigate the effect of reported childhood trauma on CSF NPY-LI in the major depressive disorder (MDD) group.

Materials and Methods

Subjects

Depressed subjects and healthy volunteers aging 18–70 yrs were recruited through advertising and referrals and admitted to a university hospital for participation in this mood disorders research. All subjects gave written informed consent as required by the Institutional Review Board. DSM-IV Axis I and Axis II disorders were diagnosed based on the structured clinical interview for DSM Axis I (First et al., 2001); and the structured clinical interview for DSM Axis II (First et al., 1997);, respectively. Healthy volunteers were free of psychiatric disorder based on the structured clinical interview for DSM non-patient version. Healthy volunteers were medication-free, had no psychiatric history based on the non-patient version of the structured clinical interview for DSM Axis I, were medically free from significant illness, and had no history of a mood or psychotic disorder in any of their first-degree relatives. All depressed subjects met DSM-IV criteria for a current major depressive episode, were free from active medical illness, and were medication-free for at least two weeks period prior to the lumbar puncture (four weeks in the case of neuroleptics and six weeks for fluoxetine). Patients with bipolar or schizophrenia spectrum disorders or those with a family history of schizophrenia or schizoaffective disorder were excluded from the study.

All subjects had a physical examination and routine laboratory tests, including a toxicological screen at baseline to rule out neurological or medical illness or illicit drugs that could affect their mental status or CSF indices.

Current severity of depression was assessed by the Hamilton Depression Rating Scale 17-item version (HDRS-17; Hamilton,

1960) that was amended to permit rating of reversed vegetative signs. A history of childhood physical or sexual abuse prior to the age of 15 was determined by specific screening questions, but duration or severity of abuse was not quantified.

Cerebrospinal Fluid Collection and Assay

On the night before the procedure, subjects had nothing but water after midnight and remained in bed from that time until the lumbar puncture was performed at about 8:00 AM. Cerebrospinal fluid was withdrawn from the L4–L5 interspace, with the subject in the left decubitus position. After the removal of 1 mL of CSF into the first sample tube, a further 15 mL of CSF was collected in the second and third tubes. These tubes were then immediately transferred onto ice water, centrifuged at 4°C, and the supernatant was pooled from the second and third tubes. The 15 mL of supernatant was divided into 1 mL aliquots for storage at -70 °C until assay. NPY-LI was assayed in duplicate in one of the 1 mL aliquots of the 15 mL sample by the radioimmunoassay as previously described (Nikisch et al., 2005). The lower level of sensitivity of the assay was 1.2 pmol/L. Intra- and inter-assay coefficients of variation were 4 and 8%, respectively. Samples were run in duplicate, the mean of which was used for statistical analyses.

Data Analysis

Diagnostic groups (MDD and healthy volunteer groups) and MDD subgroups (reported childhood abuse history versus no abuse) were characterized with respect to clinical and demographic factors. The primary outcome measure of the study was CSF NPY- LI level. The normal distribution of age, CSF concentration of NPY-LI, and HDRS-17 scores were tested by the Kolmogorov-Smirnov test. Normality in CSF NYP-LI data was achieved by square root transformation (tNPY-LI = Sqrt NPY-LI). Means are reported as value ± standard deviation. Group differences for all continuous measures were calculated by either a student's t-test or Mann–Whitney U Test. Correlation analyses were calculated using Pearson's coefficient. ANCOVA compared tNPY-LI across groups with age as a covariate. The p values are two-tailed unless otherwise specified. Statistical analyses were performed using IBM Statistics v.20 (SPSS, Inc., 2011) for Mac.

Results

Sample Characteristics

There were 81 participants enrolled in the study, including 20 healthy volunteers (mean age 34 yrs) and 61 patients with a DSM-IV diagnosis of MDD (25 MDD abuse with mean age 41 yrs and 36 MDD abuse with mean age 38 yrs, assigned based on reported childhood physical or sexual abuse). One subject was omitted from the abuse subtype analysis because information about the type of abuse was missing. There were no differences between depressed and healthy groups in terms of sex, age, and ethnicity. The HDRS-17 score was 19.6±5.5, indicating a moderate level of severity of depression.

Associations Between CSF NPY-LI Levels, MDD, and Reported Childhood Abuse

The MDD group had higher tNPY-LI level (7.9±1.5 pmol/L) compared with healthy volunteers (7.0±1.3 pmol/L, t_{79} = -2.64, p = 0.01), which remained significant when controlling for effect of age on NPY-LI ($F_{1,78}$ = 7.91, p = 0.03). Depression severity (HDRS-17) showed a modest positive correlation with tNPY-LI (r = 0.22, p = 0.04). However, there were no correlations between CSF tNPY-LI and age of MDD onset (p = 0.79) or number of episodes (p = 0.43). Positive family history (at least one family member with depression) was associated with higher HDRS-17 scores (positive family history, 19.4±6.0; no family history, 12.0±10.3; t_{78} = -3.75; p < 0.0001) and higher CSF tNPY-LI (positive family history, 8.1±1.0 pmol/L; no family history, 7.4±1.6 pmol/L; t_{78} = -2.48; p = 0.015).

Neither the presence nor the absence of childhood abuse affected CSF tNPY-LI levels (p = 0.32). However, in considering trauma subgroups, it was observed that MDD participants who reported both childhood physical and sexual abuse had higher CSF tNPY-LI compared with healthy volunteers (p < 0.0001), MDD participants who were not abused (p = 0.02), and MDD participants reporting physical abuse alone (p = 0.02, Figure 1), even after controlling for age ($F_{4,74}$ = 3.82, p = 0.007).

The rate of PTSD was higher in participants with history of abuse (29%) compared to those with no history (4.2%, $C^2(69)$ = 11.22, p = 0.004). In those with childhood abuse, tNPY-LI levels were not different between subjects who developed PTSD compared to those who did not. However, the PTSD group did show a trend for higher CSF tNPY-LI levels compared to those without PTSD (non-PTSD, 7.6±1.2 pmol/L; PTSD, 9.0±1.9 pmol/L; p = 0.062).

Given that weight and food intake may be related to NPY, we determined that weight did not differ between MDD and healthy volunteer groups or between those MDDs with or without abuse history. Within the MDD and the healthy volunteer groups, weight did not correlate with CSF tNPY-LI levels.

Discussion

We found higher CSF NPY-LI levels in medication-free, currently-depressed MDD patients compared with healthy volunteers. Age had a weak positive correlation with CSF NPY-LI level, as previously described (Taniguchi et al., 1994), but did not explain the MDD finding. Severity of depression and a positive family history of depression showed modest positive correlations with CSF NPY-LI levels. In terms of effect of childhood adversity history, we found that MDD participants who reported both physical and sexual childhood abuse had higher CSF NPY- LI. Sexual or physical abuse alone in the MDD group was not associated with elevated CSF NPY-LI. Abuse history increased the rate of co-morbid PTSD, and there was a statistical trend for higher CSF NPY-LI with comorbid PTSD. In sum, our findings suggest the predominant picture in MDD is that of higher CSF NPY-LI, it is

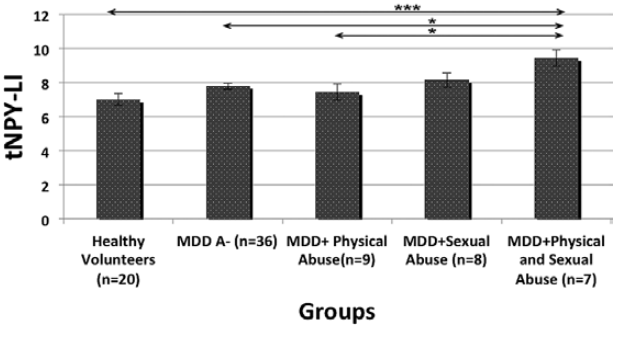

Figure 1. Transformed cerebrospinal fluid neuropeptide Y (tNPY-LI = Sqrt NPY-LI) and subtypes of childhood abuse in major depressive disorder (MDD) compared with healthy volunteers (*p < 0.05, **p < 0.0001).

correlated with depression severity, and both are related to more childhood adversity and co-morbid PTSD.

Animal models of depression, including genetic inbred models (e.g., Flinders Sensitive Line rats and Fawn Hooded rats), chronic mild stress models, the olfactory bulbectomized rat model, and maternal separation (reviewed in Heilig, 2004) have low NPY, indicating it is a biological correlate of such trait depression–like behaviors. Animal models of trait depression differ from the episodic illness course most common in MDD and our patient sample, and may have a different pathophysiology. Some animal models of depression have lower tryptophan hydroxylase levels and lower brain serotonin, whereas human MDD is characterized by over-expression of this enzyme and more serotonin in the brainstem (Bach et al., 2011). Perhaps the NPY findings in rodent depression models also do not apply to MDD. Conversely, antidepressant drugs, lithium, or electroconvulsive stimuli increase NPY-LI and NPY mRNA expression in discrete brain regions (Heilig et al., 1988; Wu et al., 2011).

The clinical studies of CSF NPY in MDD are not in agreement. Some clinical studies are consistent with our findings (Berrettini et al., 1987; Traskman-Bendz et al., 1992; Hou et al., 2006; Martinez et al., 2012). One patient study did not find CSF NPY-LI differences between MDD and non-MDD (Traskman-Bendz et al., 1992); neither did a postmortem study of major depression and NPY-LI (Ordway et al., 1995).

A comparison of 40 severely-depressed, drug-free subjects with 40 healthy volunteers found no group differences but reported a higher level of NPY-LI in recurrent MDD compared with the first episode of MDD, and concluded that higher CSF NPY-LI could be indicative of adaptation to multiple depressive episodes. Our study population mostly had multiple episodes of major depression. Higher NPY-LI was also found in 18 MDD patients compared with 25 healthy subjects (Martinez et al., 2012). Thus, these two studies support our findings of higher CSF NPY-LI in major depression.

Other studies (Table 1) reported low CSF or plasma NPY-LI levels in depression (Heilig, 2004; Nikisch et al., 2005, 2012; Nikisch and Mathe, 2008) and in bipolar disorder (Caberlotto and Hurd, 1999).

Antidepressant treatments, such as citalopram or electroconvulsive therapy, increase CSF NPY-LI levels in major depression (Nikisch et al., 2005, 2012; Nikisch and Mathe, 2008) and clinical improvement correlates with the increase in CSF NPY-LI level.

NPY may be altered as a result of childhood adversity, analogous to the stress response recalibration reported for the hypothalamic pituitary adrenal axis and the noradrenergic system. CRH receptor mRNA and NPY Y1 and Y2 receptor mRNA are expressed throughout the amygdala (Heilig, 2004), where stressful sensory inputs are integrated leading to an initiation of the stress response. Rapid activation of CRH in the central nucleus of the amygdala during the initial phase of stress response is followed by a slower activation of NPY, perhaps in order to oppose the maladaptive consequences of excessive or prolonged CRH activation. Maintaining a balance between the CRH and NPY systems might be critical for a normal physiological function and psychological state and for avoiding psychopathology (summarized in Valdez and Koob, 2004). An anxiolytic effect of NPY has been observed in animal models, such as the elevated plus-maze (Broqua et al., 1995), social interaction test (File, 1980), light-dark compartment test (Pich et al., 1993), and fear-potentiated startle model (Broqua et al., 1995). Maternal separation in rodents alters adult brain NPY expression, resulting in lower NPY levels in the hippocampus and occipital cortex and higher NPY levels in the hypothalamus; chronic treatment with lithium ameliorates these changes (Jimenez-Vasquez et al., 2001; Husum and Mathe, 2002). Chronic stress, raises amygdala NPY mRNA levels as an adaptive response (Thorsell et al., 1999). Human studies have shown increases in plasma NPY in response to acute uncontrollable stress (Heilig, 2004). Higher NPY concentrations are associated with increased resilience and less psychological distress, and combat-related PTSD patients have lower baseline NPY plasma levels compared with healthy non-traumatized subjects (Morgan et al., 2000).

Higher NPY level might therefore be a compensatory mechanism in some patients and lower levels may indicate an impaired stress response in others, including some who develop PTSD. Our results indicate higher CSF NPY-LI levels in major depression, indicating the NPY-LI related stress response may be intact but insufficient for preventing episodes of major depression. Our finding of a positive correlation of CSF NPY-LI with both severity of depression and a family history of major depression is also consistent with a model proposing that higher CSF NPY-LI levels are a response to the stress of recurrent major depression in a group with familial depression. Figure 2 shows a model of adequate resilience response, but we did not study healthy resilient subjects with a past history of childhood adversity to determine if their NPY levels were even higher and thereby accounted for their resilience.

Despite the relationship of NPY to food intake and weight (Stanley et al., 1986), we found no such relationship in either MDD or healthy volunteers, and weight did not explain our findings.

We did not find a simple effect of the presence or absence of reported childhood abuse on CSF NPY-LI levels. However, we found that the co-occurrence of childhood physical and sexual abuse was associated with higher levels of NPY-LI (Figure 1). Therefore, increased expression of NPY in the brain may reflect a homeostatic response to the exposure of a greater allostatic load of multiple types of early childhood trauma. Thus, there may be different phenocopies of major depression: one that is primarily genetic and has an intact or robust NPY stress response and a second that is primarily a major depression where a less robust NPY response to MDD indicates an impaired NPY stress response (Figure 2). Some studies, such as ours, mainly detected the former subtype of depression, which may involve a recurrent depression with a higher rate of positive family history, consistent with a pathogenic pathway involving genes and environment. Differences in results in the literature could be explained by the composition of the MDD study populations in terms of the proportion of NPY-sufficient and NPY-insufficient resilient response subjects (Figure 2). That may be determined by comparing laboratory stress responses or clinical differences such as in-family history of MDD, early age of onset of MDD, severity of recent stressful life events preceding the onset of an episode of major depression, and perhaps abnormalities in other stress response systems such as the hypothalamic pituitary adrenal axis.

The limitations of the current study involve a limited measure of childhood abuse based on a qualitative measurement of the presence or absence of reported physical and/or sexual trauma prior to the age of 15. Other types of trauma (e.g., neglect) were not accounted for. Using a standard trauma scale such as the Childhood Trauma Questionnaire (Bernstein et al., 1994) could add precision to the measurement of the severity of childhood adversity. Including resilient healthy controls with histories of childhood trauma would further clarify the mechanisms of the adaptive NPY response. An expanded study sample

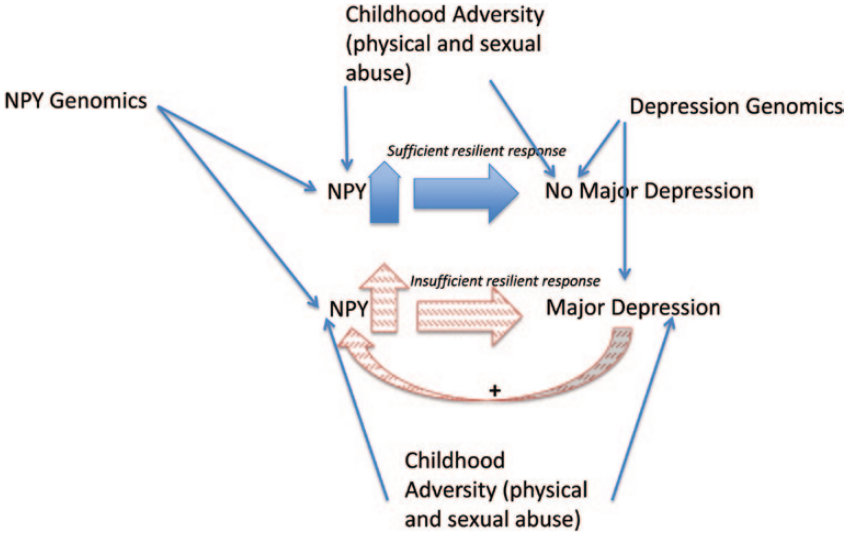

Figure 2. NPY response in major depression. High NPY levels in depressed patients may be indicative of an insufficiently resilient response to stress.

may reveal a bimodal distribution of CSF NPY where the high NPY group has a resilient response and the low NPY group has the vulnerability biological phenotype.

Acknowledgments

This study was supported by a MH062185 grant to Dr Mann and by Swedish Medical Research Council grant 10414 and support from the Karolinska Institutet to Dr Mathé. We thank Dr T. Liu for technical assistance.

Statement of Interest

Dr Mathé and Dr Soleimani report no potential conflicts of interest. Dr Mann receives royalties for commercial use of the C-SSRS from the Research Foundation for Mental Hygiene and has stock options in Qualitas Health, which is developing an EPA supplement. Dr Oquendo receives royalties for the use of the Columbia Suicide Severity Rating Scale. She has received unrestricted educational grants and/or lecture fees from Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Otsuko, Pfizer, Sanofi-Aventis, and Shire. Her family owns stock in Bristol Myers Squibb. Dr Sullivan is a Scientific Advisory Board member and consultant for Tonix Pharmaceuticals, Inc.

References

Bach H, Arango V, Huang YY, Leong S, Mann JJ, Underwood MD (2011) Neuronal tryptophan hydroxylase expression in BALB/cJ and C57Bl/6J mice. J Neurochem 118:1067–1074.

Baker DG, et al. (2013) Characterization of cerebrospinal fluid (CSF) and plasma NPY levels in normal volunteers over a 24-h timeframe. Psychoneuroendocrinology 38:2378–2382.

Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Sapareto E, Ruggiero J (1994) Initial reliability and validity of a new retrospective measure of child abuse and neglect. American J Psych 151:1132–1136.

Berrettini WH, Doran AR, Kelsoe J, Roy A, Pickar D (1987) Cerebrospinal fluid neuropeptide Y in depression and schizophrenia. Neuropsychopharmacology 1:81–83.

Broqua P, Wettstein JG, Rocher MN, Gauthier-Martin B, Junien JL (1995) Behavioral effects of neuropeptide Y receptor agonists in the elevated plus-maze and fear-potentiated startle procedures. Behav Pharmacol 6:215–222.

Caberlotto L, Hurd YL (1999) Reduced neuropeptide Y mRNA expression in the prefrontal cortex of subjects with bipolar disorder. Neuroreport 10:1747–1750.

Cervilla JA, Molina E, Rivera M, Torres-Gonzalez F, Bellon JA, Moreno B, Luna JD, Lorente JA, Mayoral F, King M, Nazareth I, Group PSC, Gutierrez B (2007) The risk for depression conferred by stressful life events is modified by variation at the serotonin transporter 5HTTLPR genotype: evidence from the Spanish PREDICT-Gene cohort. Mol Psychiatry 12:748–755.

Cohen H, Liu T, Kozlovsky N, Kaplan Z, Zohar J, Mathe AA (2012) The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. Neuropsychopharmacology 37:350–363.

Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP (1996) A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry 1:453–460.

File SE (1980) The use of social interaction as a method for detecting anxiolytic activity of chlordiazepoxide-like drugs. J Neurosci Methods 2:219–238.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997) Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, DC: American Psychiatric Press, Inc.

First MB, Spitzer RL, Gibbon M, Williams AR (2001) Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version–Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute, Biometrics Research.

Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.

Heilig M (2004) The NPY system in stress, anxiety and depression. Neuropeptides 38:213–224.

Heilig M, Wahlestedt C, Ekman R, Widerlov E (1988) Antidepressant drugs increase the concentration of neuropeptide Y (NPY)-like immunoreactivity in the rat brain. Eur J Pharmacol 147:465–467.

Hou C, Jia F, Liu Y, Li L (2006) CSF serotonin, 5-hydroxyindolacetic acid and neuropeptide Y levels in severe major depressive disorder. Brain Res 1095:154–158.

Husum H, Mathe AA (2002) Early life stress changes concentrations of neuropeptide Y and corticotropin-releasing hormone in adult rat brain. Lithium treatment modifies these changes. Neuropsychopharmacology 27:756–764.

Jimenez Vasquez PA, Salmi P, Ahlenius S, Mathe AA (2000) Neuropeptide Y in brains of the Flinders Sensitive Line rat, a model of depression. Effects of electroconvulsive stimuli and d-amphetamine on peptide concentrations and locomotion. Behav Brain Res 111:115–123.

Jimenez Vasquez PA, Mathe AA, Thomas JD, Riley EP, Ehlers CL (2001) Early maternal separation alters neuropeptide Y concentrations in selected brain regions in adult rats. Dev Brain Res 131:149–152.

Martinez JM, Garakani A, Yehuda R, Gorman JM (2012) Proinflammatory and "resiliency" proteins in the CSF of patients with major depression. Depress Anxiety 29:32–38.

Morgan CA 3rd, Wang S, Southwick SM, Rasmusson A, Hazlett G, Hauger RL, Charney DS (2000) Plasma neuropeptide-Y concentrations in humans exposed to military survival training. Biol Psychiatry 47:902–909.

Nikisch G, Agren H, Eap CB, Czernik A, Baumann P, Mathe AA (2005) Neuropeptide Y and corticotropin-releasing hormone in CSF mark response to antidepressive treatment with citalopram. Int J Neuropsychop 8:403–410.

Nikisch G, Baumann P, Liu T, Mathe AA (2012) Quetiapine affects neuropeptide Y and corticotropin-releasing hormone in cerebrospinal fluid from schizophrenia patients: relationship to depression and anxiety symptoms and to treatment response. Int J Neuropsychop 15:1051–1061.

Nikisch G, Mathe AA (2008) CSF monoamine metabolites and neuropeptides in depressed patients before and after electroconvulsive therapy. Eur Psychiatry 23:356–359.

Ordway GA, Stockmeier CA, Meltzer HY, Overholser JC, Jaconetta S, Widdowson PS (1995) Neuropeptide Y in frontal cortex is not altered in major depression. J Neurochem 65: 1646–1650.

Pich EM, Agnati LF, Zini I, Marrama P, Carani C (1993) Neuropeptide Y produces anxiolytic effects in spontaneously hypertensive rats. Peptides 14:909–912.

Sah R, Ekhator NN, Strawn JR, Sallee FR, Baker DG, Horn PS, Geracioti TD Jr. (2009) Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder. *Biol Psychiatry* 66:705–707.

Stanley BG, Kyrkouli SE, Lampert S, Leibowitz SF (1986) Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity. Peptides 7:1189–1192.

Taniguchi S, Yanase T, Kurimoto F, Takayanagi R, Haji M, Kurose S, Nawata H (1994) Age-related increase in neuropeptide Y-like immunoreactivity in cerebrospinal fluid in women. Fukuoka Igaku Zasshi 85:361–365.

Thorsell A, Carlsson K, Ekman R, Heilig M (1999) Behavioral and endocrine adaptation, and up-regulation of NPY expression in rat amygdala following repeated restraint stress. Neuroreport 10:3003–3007.

Traskman-Bendz L, Ekman R, Regnell G, Ohman R (1992) HPA-related CSF neuropeptides in suicide attempters. Eur Neuropsychopharmacol 2:99–106.

Valdez GR, Koob GF (2004) Allostasis and dysregulation of corticotropin-releasing factor and neuropeptide Y systems: implications for the development of alcoholism. Pharmacol Biochem Behav 79:671–689.

Widerlov E, Lindstrom LH, Wahlestedt C, Ekman R (1988) Neuropeptide Y and peptide YY as possible cerebrospinal fluid markers for major depression and schizophrenia, respectively. *J Psychiatr Res* 22:69–79.

Wilkinson PO, Goodyer IM (2011) Childhood adversity and allostatic overload of the hypothalamic-pituitary-adrenal axis: a vulnerability model for depressive disorders. Dev Psychopathol 23:1017–1037.

Wu G, Feder A, Wegener G, Bailey C, Saxena S, Charney D, Mathe AA (2011) Central functions of neuropeptide Y in mood and anxiety disorders. Expert Opin Ther Targets 15:1317–1331.