Brief Report

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

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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 post-traumatic 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...
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.
The MDD group had higher tNPY-LI level (7.9 ± 1.5 pmol/L) compared with healthy volunteers (7.0 ± 1.3 pmol/L, \( t_{78} = -2.64, p = 0.01 \)), 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, we found 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 (\( F_{1,78} = 3.82, p = 0.007 \)).

The rate of PTSD was higher in participants with history of abuse (29%) compared to those with no history (4.2%, \( C(69) = 11.22, p = 0.004 \)). 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...
correlated with depression severity, and both are related to more childhood adversity and co-morbid HPA dysfunction (File, 1980) light-dark compartment test (File, 1980), social interaction test (File, 1980), and fear-potentiated startle test (Pich et al., 1993), and fear-potentiated startle model (Broqua et al., 1995). Maternal separation in rodents alters 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 the 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 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 of resilient subjects with a past history of childhood adversity to determine if their NPY levels were even higher and thereby accounted for their resilience.

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
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.

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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, Otsuka, 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.

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