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Decreased Expression of Nociceptin/Orphanin FQ in the dorsal Anterior Cingulate Cortex of Suicides

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Abstract

The nociceptin/orphanin FQ (N/OFQ) – Nociceptin Opiod-like Peptide (NOP) receptor system is a critical mediator of physiological and pathological processes involved in emotional regulation and drug addiction. As such, this system may be an important biological substrate underlying psychiatric conditions that contribute to the risk of suicide. Thus, the goal of the present study was to characterize changes in human N/OFQ and NOP signaling as a function of depression, addiction and suicide. We quantified the expression of N/OFQ and NOP by RT-PCR in the anterior insula, the mediodorsal thalamus, and the dorsal anterior cingulate cortex (dACC) from a large sample of individuals who died by suicide and matched psychiatrically-healthy controls. Suicides displayed an 18% decrease in the expression of N/OFQ in the dACC that was not accounted for by current depressive or substance use disorders at the time of death. Therefore, our results suggest that dysregulation of the N/OFQ-NOP system may contribute to the neurobiology of suicide, a hypothesis that warrants further exploration.

Introduction

The nociceptin/orphanin FQ (N/OFQ) peptide and Nociceptin Opioid-like Peptide Receptor (NOP) belong to the opioid family of peptidergic neuromodulators. Under physiological conditions, N/OFQ selectively binds to and activates the NOP, an inhibitory G-protein coupled receptor that decreases neuronal excitability (Zollner and Stein, 2007). Although the 2 genes show strong homology with other genes coding for opioid peptides and receptors, pharmacological studies indicate that the N/OFQ-NOP signaling pathway forms a distinct process within the opioid system (Zollner and Stein, 2007).

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Author Disclosures

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Over the last few years, it has been shown that N/OFQ and NOP are widely distributed in the central nervous system and are implicated in several physiological and pathological processes (Lambert, 2008). In particular, the role of this system has been explored in the context of animal models of emotional dysregulation (most notably using stress paradigms) and exposure to drugs of abuse (see (Mallimo and Kusnecov, 2013; Witkin et al., 2014) for recent reviews). In humans, genetic (Andero et al., 2013) and imaging (Lohith et al., 2012) studies began only recently to test the translational relevance of these findings with one postmortem study that focused on alcohol abuse (Kuzmin et al., 2009). Importantly, while depression and substance use disorders represent strong lifetime risk factors for the emergence of suicidal behaviors (Turecki, 2014), the potential implication of the N/OFQ-NOP pathway in the neurobiology of suicide remains to be explored.

The goal of the present study was to characterize changes in human N/OFQ-NOP signaling as a function of depression, addiction, and suicide. Using postmortem brain tissue, we quantified the expression of these 2 genes in a large sample of suicides that were affected by major depressive disorder and/or substance use disorders. We focused our analyses on three brain regions: the anterior insula (AI), the mediodorsal thalamus (MDT), and the dorsal anterior cingulate cortex (dACC). The AI represents a brain hub where interoceptive and sensory stimuli are interpreted in terms of emotional states (Nieuwenhuys, 2012), and where neuronal activity was found to correlate, following traumatic life experiences, with genetic variation in the NOP gene (Andero et al., 2013). The MDT is a structure where changes in the endogenous activity of the opioid system (in particular the mu opioid receptor) have been documented in depressed subjects (Kennedy et al., 2006), as well as following exposure to aversive stimuli (e.g., social rejection tasks (Way et al., 2009)). Finally, the dACC plays a well-known central role in emotional regulation in both human and rodent species (Etkin et al., 2011; Willner et al., 2013).

Overall, our findings indicate that suicide significantly associates with a downregulation of N/OFQ in the dACC, while depression and substance use disorder have no significant effect in this association. Therefore, this study suggests that the N/OFQ-NOP system may play a role in suicide risk.

Experimental Procedures

Clinical sample

This study included (i) subjects who died by suicide (cases) and (ii) subjects who died suddenly, without a prolonged agonal state or protracted medical illness, e.g. from accidents (controls). Psychiatric diagnoses were elicited following proxy-based, structured interviews completed with best informants, as described elsewhere (Dumais et al., 2005). Sample characteristics for cases and controls from the AI, MDT, and dACC brain regions are presented in Table 1. As dysregulation of the N/OFQ-NOP system has been primarily documented in animal models of mood or substance use disorder, we examined a sample including subjects with either one or two of these diagnoses. Case and control groups were matched for sex, age, postmortem interval (PMI), brain pH, and RNA integrity number (RIN). Postmortem brain samples were obtained from the Douglas-Bell Canada Brain Bank (http://douglasbrainbank.ca/). Briefly, samples of the three brain regions (AI, dACC, and

MDT) were dissected from each subject from 0.5 cm-thick coronal brain sections by expert brain bank staff following standard dissection procedures and with the aid of a human brain atlas ((Mai et al., 2007), and http://www.thehumanbrain.info/brain/bn_brain_atlas/brain.html). For the AI, the superior part of the insula was dissected just beneath the overlying opercula in the brain section containing the striatum at the level of nucleus accumbens. MDT samples were obtained by dissecting the dorsal part of the thalamus (1/3 upper part of thalamus), medially to the internal medullary lamina found in sections equivalent to plates 40 to 43 of the atlas (23.9 to 27.8mm from the center of the anterior commissure). Finally, the dACC was dissected in sections equivalent to plates 15 to 28 of the atlas (−7.5 to 8.0mm from the center of the anterior commissure), and grey matter was taken immediately dorsal to the corpus callosum.

RT-PCR analysis of gene expression

RNA was extracted from homogenized brain samples using the RNeasy Lipid Tissue Mini Kit (Qiagen). RNA quantity and quality were measured by Nanodrop® and Agilent 2100 Bioanalyzer technologies, and only samples with a RNA integrity number (RIN) greater than 5 were used. Extracted RNA was reverse-transcribed using M-MLV reverse transcriptase (Invitrogen™). mRNA levels were quantified by real time polymerase chain reaction (RT-PCR) using SYBR® Green DNA intercalating dye and master mix (Bio-Rad) and the ABI 7900HT PCR machine. Primers for targeted genes were designed using Primer-BLAST (http://www.ncbi.nlm.nih.gov/tools/primer-blast/), and validated by gel migration and dissociation curves. Complementary DNAs from every subject were pooled and used to prepare calibration curves, from which cDNA quantities of target genes were calculated in each sample according to the measured RT-PCR threshold cycle (Ct value). Relative expression levels for each gene of interest were calculated by dividing the cDNA quantity for the gene of interest by the arithmetic mean of cDNA quantities for two reference housekeeping genes (GAPDH and β-actin).

Statistical analyses

Statistical analyses were carried out by the IBM SPSS (statistical package for the social sciences) package. A general linear model was used to analyze group differences of gene expression, as a function of histories of depression, substance use disorder and suicide. Potential correlations between variables that commonly act as confounders (pH, post-mortem interval, PMI, RIN, and age) and gene expression level were assessed separately for each gene of interest, and only those variables showing a significant Pearson correlation were included in each final model. Residuals across levels of groups were tested for normality with the Shapiro-Wilk Test and for equal variance with Levene's test. Statistical significance was set at $p < 0.05$.

Results

Anterior insula

In the AI, age was significantly correlated with N/OFQ mRNA expression ($r = -0.496$, $N=94$, $p=0.0001$), whereby N/OFQ mRNA levels decreased as a function of increasing age (Fig. 1A). While controlling for this effect of age as a covariate, we found no main effect of

sex (F(1,91)=0.039, p=0.83), substance use disorder (SUD, (F(1,91)=1.34, p=0.25), depression (F(1,91)=0.39, p=0.54), or suicide (F(1,91)=0.029, p=0.87) on N/OFQ expression (Fig. 1B). No significant covariates were associated with NOP expression. Furthermore, there was no significant effect of sex (F(1,92)=0.29, p=0.60), SUD (F(1,92)=0.38, p=0.54), depression (F(1,92)=0.005, p=0.94), or suicide (F(1,92)=0.15, p=0.70) on NOP expression (Fig. 1C). Altogether, sex, SUD, depression, and suicide were not associated with differences in N/OFQ or NOP expression in the AI.

Mediodorsal thalamus

Contrasting with our results in the AI, age had no significant effect on N/OFQ expression in the MDT, indicating that age-dependent regulation of this gene expression is brain region-specific. As well, no other possible confounding factors were found to be associated with N/OFQ expression. There was no significant effect of sex (F(1,80)=0.25, p=0.62), SUD (F(1,80)=0.47, p=0.50), depression (F(1,80)=1.006, p=0.32), or suicide (F(1,80)=0.45, p=0.51) (Fig. 2A) on N/OFQ expression. NOP mRNA expression was significantly correlated with pH (r= 0.335, N=82, p=0.002), with increased expression of the receptor as a function of increasing pH (data not shown). However, there was no significant main effect of sex (F(1,79)=0.12, p=0.73), SUD (F(1,79)=0.92, p=0.34), depression (F(1,79)=0.51, p=0.48), or suicide (F(1,79)=1.32, p=0.26) (Fig. 2B) on NOP expression, while controlling for pH as a covariate. Thus, sex, SUD, depression, and suicide did not affect N/OFQ or NOP expression in the MDT.

Dorsal anterior cingulate cortex

In the dACC, similar to our AI findings, age was significantly correlated with N/OFQ expression (r=−0.298, N=80, p=0.007) in the same direction, whereby N/OFQ levels decreased as a function of increasing age (Fig.3A). Although there was no significant effect of sex (F(1,77)=1.68, p=0.20), SUD (F(1,77)=1.82, p=0.18) or depression (F(1,77)=2.58, p=0.11) on N/OFQ expression, there was a significant effect of suicide (F(1,77)=4.21, p=0.044), while controlling for age as a covariate. Accordingly, suicide completers (N=54) showed an 18% decrease in N/OFQ mRNA expression levels compared to controls (Fig. 3B). RIN was significantly correlated with NOP mRNA expression (r=0.430, N=80, p<0.0001), whereby NOP levels increased as a function of increasing RIN values (data not shown). However, there was no significant effect of sex (F(1,77) =0.63, p=0.43), SUD (F(1,77)=2.00, p=0.16), depression (F(1,77)=0.055, p=0.82), or suicide F(1,77)=0.077, p=0.78) (Fig. 3C) on the expression of NOP levels. Therefore, sex, SUD, depression, and suicide did not affect the expression of NOP mRNA in the dACC.

Discussion

The N/OFQ-NOP system and substance use disorders

There is strong evidence from the pre-clinical literature supporting the notion that the N/OFQ-NOP system may be involved in regulating drug-taking and addictive behaviors (Witkin et al., 2014). Results from rodent studies are consistent and mainly indicate that NOP activity blunts reinforcing and other behavioral properties of several drugs of abuse, including opiates, alcohol and psychostimulants (Witkin et al., 2014). In humans, a study

examining postmortem samples from alcoholics reported decreased levels of N/OFQ mRNA in the hippocampus, and decreased NOP mRNA in the central amygdala (Kuzmin et al., 2009). In contrast, the present study found no evidence for differential expression of either N/OFQ or NOP across 3 other brain regions. Therefore, it is likely that exposure to drugs of abuse leads to brain region-specific dysregulation of N/OFQNOP signaling. Alternatively, these transcriptomic adaptations may occur following chronic consumption of ethanol, but not other drugs of abuse. Accordingly, it is important to acknowledge that the aforementioned study (Kuzmin et al., 2009) was performed in a relatively small but homogeneous cohort of alcoholics (N=15 alcoholics + N=15 controls), with a modest 20% comorbidity for nicotine addiction. Our own sample (in the dACC, N=27 SUD+ and 53 controls) was composed of (i) 56% subjects dependent on alcohol only, (ii) 22% subjects dependent on alcohol *and* another drug of abuse, and (iii) 22% dependent on other substances than alcohol. This slightly stronger heterogeneity may have hampered our ability to detect ethanol-induced changes in N/OFQ-NOP expression.

The N/OFQ-NOP system and depression

The present study did not detect any effect of depressive disorder on the expression of N/OFQ or NOP in any brain region. To our knowledge, there is currently no available data from postmortem studies documenting a transcriptional dysregulation of the N/OFQ-NOP system as a function of depression. Increased expression of NOP has only been reported using expression micro-arrays in the orbitofrontal cortex of patients with bipolar disorder (Ryan et al., 2006). Nevertheless, an extensive animal literature is available and has been reviewed recently (Gavioli and Calo, 2013; Witkin et al., 2014). Using classical rodent assays for depressive-like behaviors, systemic injections of NOP antagonists have been shown to display antidepressant-like effects (Gavioli et al., 2004; Redrobe et al., 2002), indicating that endogenous N/OFQ signaling may negatively regulate hedonic tone. Our human study, in contrast, failed to detect any difference in N/OFQ-NOP expression in the dACC, AI or MDT, suggesting that the potential NOP-dependant mood regulation may occur in other brain regions. Future animal studies manipulating N/OFQ-NOP activity locally within specific brain-regions (Goeldner et al., 2010) should allow to clarify the mechanisms underlying emotional regulation by this system.

The N/OFQ-NOP system and suicide

Previous post-mortem and imaging studies suggested that adaptations at the level of mu (Gabilondo et al., 1995; Gross-Isseroff et al., 1990; Kennedy et al., 2006; Scarr et al., 2012) or kappa (Hurd, 2002; Pietrzak et al., 2014) opioid receptors signaling may contribute to suicide pathophysiology. Extending on these findings, the present study shows that suicide completers exhibit decreased levels of N/OFQ mRNA in the dACC, compared to non-suicidal control subjects. Although a majority of suicide completers were comorbid with depression or SUD, our results suggest that the difference in N/OFQ expression is specific to suicide. Over the last decades, intensive research efforts have started unraveling behavioural and neurobiological traits of the suicidal brain (Turecki, 2014). Studies have implicated HPA axis dysregulation (Oquendo et al., 2014), impulsive-aggressive traits (Dumais et al., 2005), and impaired decision-making (Jollant et al., 2005) in the neurobiology of suicide. Importantly, the dACC represents a crucial brain area for negative feedback mechanisms

controlling the HPA axis, as well as for cognitive processes. In rodent studies, regulation of the HPA axis by N/OFQ and NOP has been largely investigated, but results are conflicting. For example, acute stressors in rat lead to either decreased (in the basal forebrain, see (Devine et al., 2003)) or increased (in the hippocampus, see (Nativio et al., 2012)) expression of the N/OFQ peptide. Furthermore, chronic stress had no effect (Devine et al., 2003) or lead to increased expression of the NOP receptor (Green and Devine, 2009). Altogether, these results suggest that different stressors, depending on their intensity, duration and modality, may have opposite effects on N/OFQ-NOP activity across different brain regions, with either potentially beneficial adaptive values or detrimental consequences. Within this line, the decreased N/OFQ expression that we observed in the dACC may contribute to the hypersensitivity of the HPA axis and decreased coping capabilities that have been associated with suicide risk. However, it is also possible that these changes represent a beneficial adaptive mechanism which ultimately failed to compensate for other detrimental factors contributing to the precipitation of suicide. Beyond the HPA axis, another appealing possibility is that decreased N/OFQ expression in the dACC may mediate other pathological dimensions of suicidality, such as decision-making and the regulation of aggressive and impulsive behaviors. Robust and validated animal models are available and should allow exploring these potentially new and exciting facets of N/OFQ physiology.

The present study is not without limitation. Depression represents a major contributor to the risk of suicide, and dissociating underlying neurobiological mechanisms is a difficult task. Within this line, there is a significant overlap between depression and suicide in our cohort, and future studies will be necessary to confirm the specific role of N/OFQ in suicide. While the psychological autopsy procedure allows for a reliable retrospective assessment of psychiatric histories, it remains possible that in our cohort the presence of depressive symptoms at the time of death may not have been captured in a subset of suicide completers. In that scenario, we speculate that decreased N/OFQ expression in the dACC may not only associate with suicide, but more generally with mood dysregulation as well. Another potential confounding factor to take into account is the acute pharmacological effects of drugs taken before death, especially opiates. However, this factor is unlikely to be meaningful in the present study. Indeed, toxicological screenings (in urine and blood) found traces of opiates in only 4 suicide completers. Expression of N/OFQ was not significantly decreased in these 4 subjects compared to the rest of the cohort (data not shown), and the detected compounds (codeine, morphine, methadone and oxycodone) are primarily considered as agonists at the mu opioid, but not the NOP, receptor. Finally, while our study explored a large cohort of subjects, we found a modestly significant association between suicide and N/OFQ expression that could be detected in only one brain region. Therefore, we cannot exclude the possibilities that this effect may be due to unidentified confounding factors, or may represent a minor contributor to the risk of suicide.

In conclusion, this study presents the first preliminary evidence suggesting that the N/OFQ peptide is dysregulated in suicide completers, thereby potentially contributing to impaired emotional and behavioral control and, ultimately, to the suicidal crisis. Further experiments are needed to understand how N/OFQ signaling in the dACC may interact with other brain circuits as well as behavioral traits implicated in suicidality.

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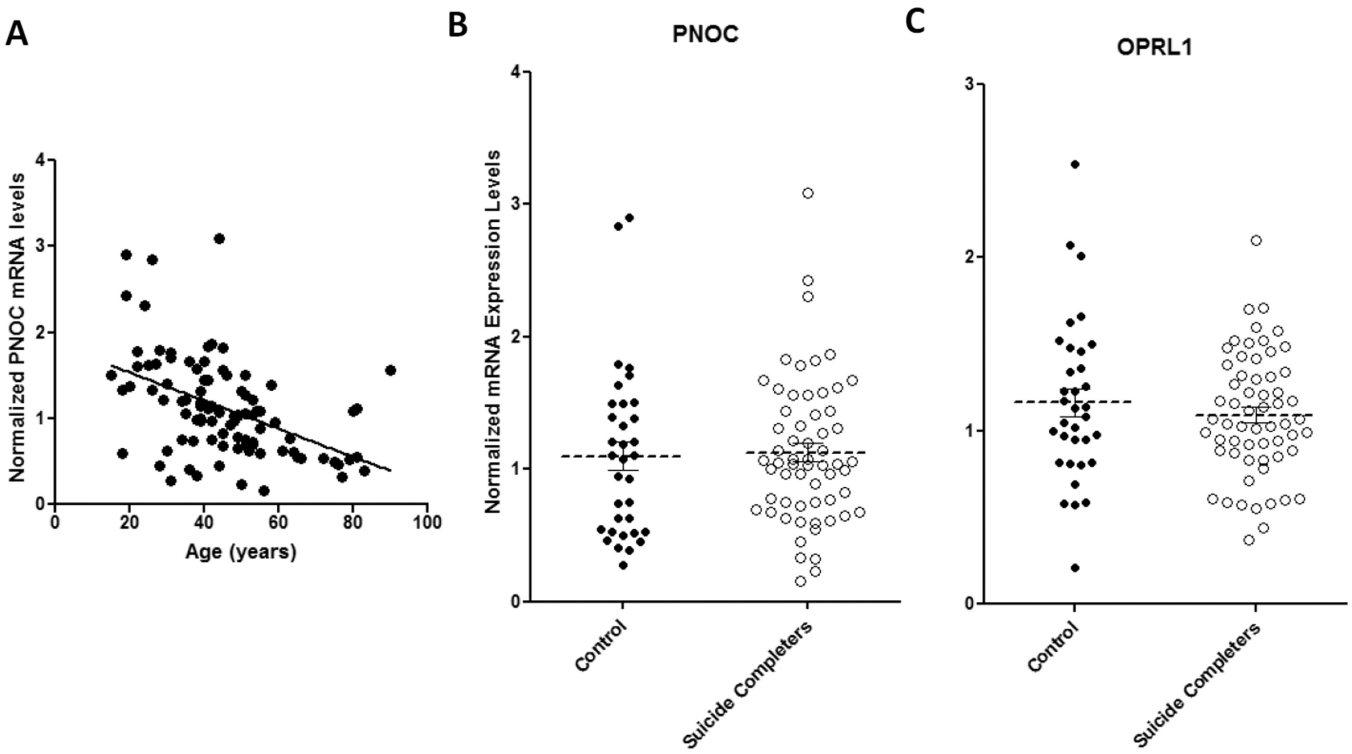

Fig. 1.

PNOC and OPRL1 genes encode the nociceptin/orphanin FQ peptide and the Nociceptin Opioid-like Peptide Receptor, respectively. Age was significantly correlated with PNOC expression level (A) in the Anterior Insula (AI) (r=−0.468, p=0.0001). There was no significant effect of suicide on expression levels of PNOC (B) or OPRL1 (C) mRNA in the AI. Mean values and standard error bars are shown.

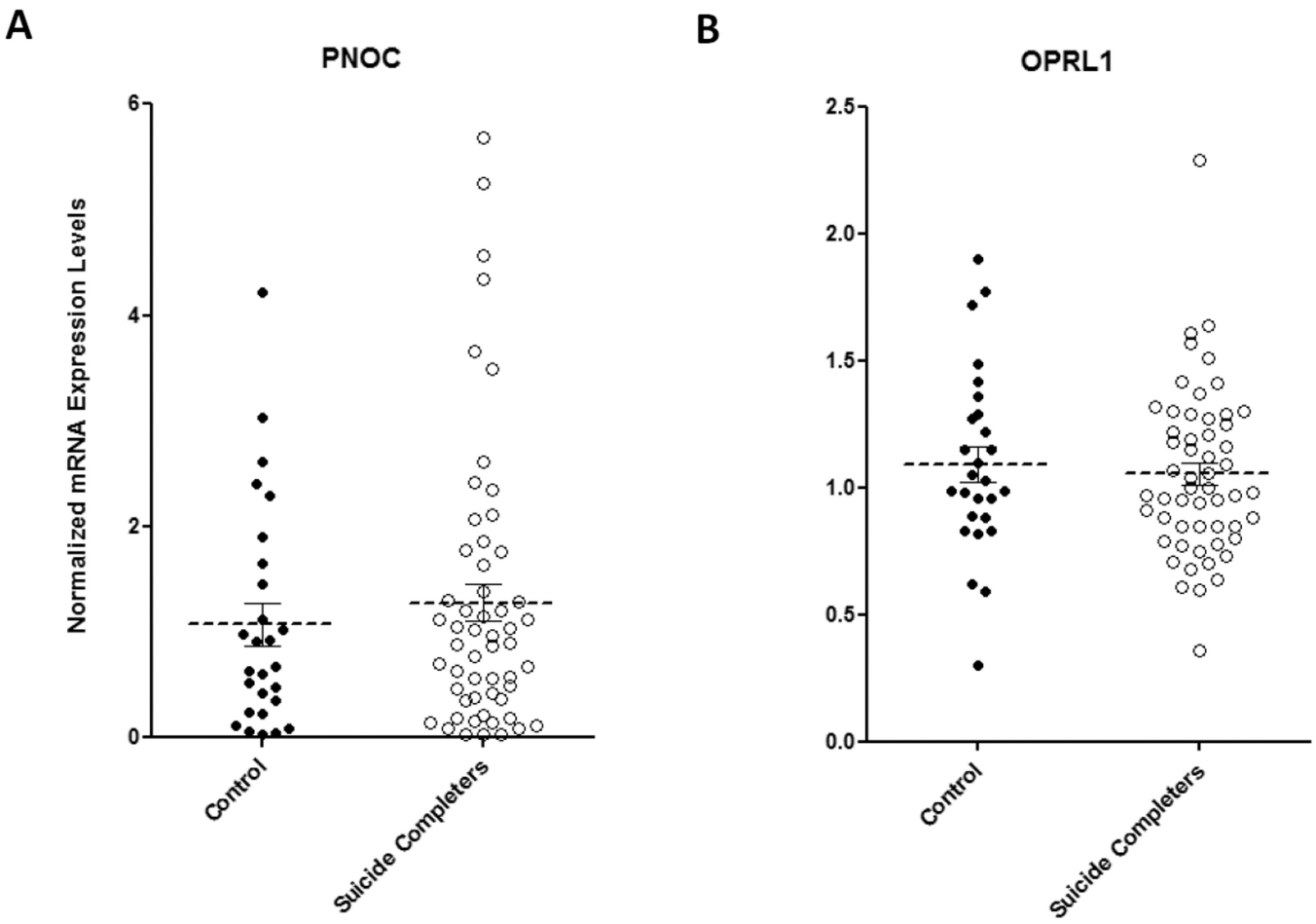

Fig. 2.

PNOC and OPRL1 genes encode the nociceptin/orphanin FQ peptide and the Nociceptin Opioid-like Peptide Receptor, respectively. There was no significant effect of suicide on expression levels of PNOC (A) or OPRL1 (B) mRNA in the mediodorsal thalamus. Mean values and standard error bars are shown.

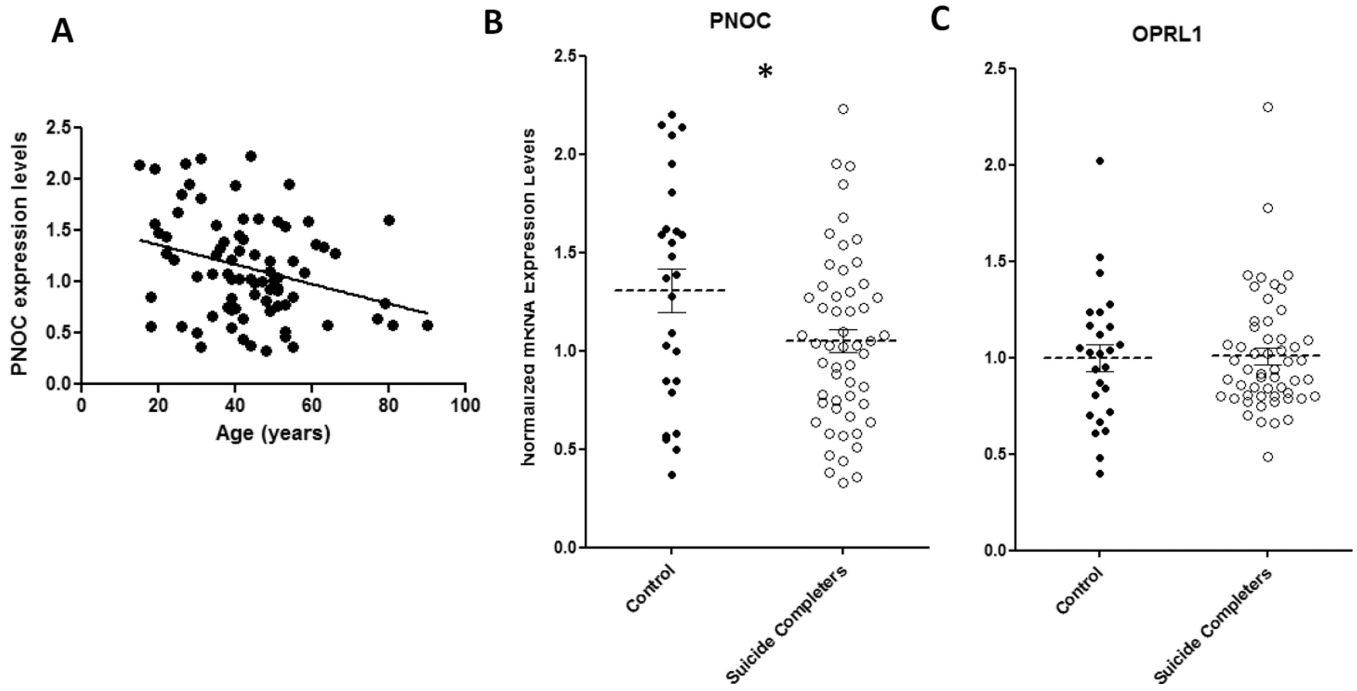

Fig. 3.

PNOC and OPRL1 genes encode the nociceptin/orphanin FQ peptide and the Nociceptin Opioid-like Peptide Receptor, respectively. Age was significantly correlated with PNOC expression level (A) in the dorsal anterior cingulate cortex (r=−0.299, p=0.007). Suicide completers showed an 18% decrease (p<0.05) in PNOC expression levels compared to controls (B), controlling for the effects of age. There was no effect of suicide on OPRL1 mRNA expression levels (C). Mean values and standard error bars are shown.

Table 1

Sample Demographics.

Anterior Insula			
Characteristics	Control (N=34)	Suicides (N=60)	p-value
Male/Female	29/5	48/12	0.59
Age (years)	45.68±3.60	45.23±1.77	0.57
PMI (hours)	23.87±3.17	26.78±2.69	0.43
Brain pH	6.48±0.05	6.59±0.04	0.10
RIN	6.86±0.16	7.15±0.13	0.38
Mood Disorder	6 (18%)	50 (83%)	<0.001
Substance Use Disorder	7 (21%)	27 (45%)	0.015
Mediodorsal Thalamus			
Characteristics/Diagnosis	Controls (N=27)	Suicides (N=55)	p-value
Male/Female	23/4	44/11	0.43
Age (years)	43.81±3.62	44.93±1.88	0.37
PMI (hrs)	25.04±3.40	24.95± 2.66	0.88
Brain pH	6.51±0.06	6.63±0.04	0.09
RIN	5.96±0.10	6.47±0.11	0.41
Mood Disorder	4 (15%)	46 (84%)	<0.001
Substance Use Disorder	4 (15%)	25 (45%)	0.016
Dorsal Anterior Cingulate Cortex			
Characteristics	Controls (N=26)	Suicides (N=54)	p-value
Male/Female	23/3	44/10	0.57
Age (years)	41.27±3.55	44.59±1.91	0.76
PMI (hours)	24.83±3.51	25.54±2.67	0.99
Brain pH	6.51+0.06	6.63±0.04	0.08
RIN	6.19±0.16	6.34±0.10	0.84
Mood Disorder	3 (12%)	46 (85%)	< 0.001
Substance Use Disorder	4 (15%)	23 (43%)	0.006