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Amygdalar expression of proteins associated with neuroplasticity in major depression and suicide

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ABSTRACT

Introduction: Doublecortin (DCX) and polysialilated neural cell adhesion molecule (PSA-NCAM), two proteins associated with immature neuronal phenotypes and elevated neuroplasticity in the adult brain, have recently been identified in the mammalian amygdala, and evidence from rodent studies suggests that stress may modify their expression in this brain region. The purpose of the present study was to investigate whether the expression of proteins involved in neuroplasticity is altered in the amygdala of individuals with depression.

Methods: Basolateral amygdala (BLA) and central amygdala (CeA) postmortem human brain samples were collected from individuals with a history of depression ($n = 22$ and 25, respectively) and psychiatrically healthy controls (CTRL; $n = 14$). Proteins associated with neuroplasticity were quantified using Western blotting.

Results: Immunoblots revealed that depressed subjects displayed increased expression of DCX ($p = 0.033$) and PSA-NCAM ($p = 0.027$) in the BLA as compared to CTRLs. Subsequent analyses revealed that this effect was due primarily to a subset of depressed subjects who had not died by suicide (DNS). DNS subjects displayed higher DCX than CTRLs ($p < 0.001$) and depressed suicides ($p = 0.001$), and higher PSA-NCAM than CTRLs ($p = 0.007$). Conversely, within the CeA, DNS subjects displayed a tendency toward lower DCX expression than CTRLs ($p = 0.062$), and higher BDNF levels than DS subjects ($p = 0.045$).

Conclusion: These results suggest that the BLA and CeA display contrasting patterns of neuroplasticity in depression, and that greater impairment of amygdalar neuroplasticity may be associated with increased risk of suicide.

1. Introduction

Adult brain neurogenesis, the process of proliferation, migration, differentiation, and functional integration of newborn neurons into mature neural circuits, has received increasing attention since its demonstration in humans (Eriksson et al., 1998), and has since become one of the most scrutinized forms of neuroplasticity in the adult mammalian brain. Among mammals, two brain regions are generally accepted to retain a neurogenic potential throughout life: the olfactory bulb, which receives a constant supply of postmitotic cells born in the subventricular zone of the lateral ventricle (SVZ) or in the rostral migratory stream, and the dentate gyrus of the hippocampus (Eriksson et al., 1998; Bédard and Parent, 2004). Based mainly on animal studies showing that various stressors decrease adult hippocampal neurogenesis (AHN) (Gould et al., 1998; Pham et al., 2003), whereas antidepressant treatments (ADT) increase AHN (Malberg et al., 2000; Perera et al., 2007), an implication of this phenomenon in the etiology of depression and ADT response has been hypothesized (Dranovsky and Hen, 2006; Sahay and Hen, 2007). The very few postmortem studies carried out to examine these hypotheses have so far provided some support. In particular, the elegant work of Boldrini and colleagues has recently indicated that ADTs stimulate both cell proliferation and angiogenesis in the human dentate gyrus (Boldrini et al., 2009, 2012).

However, studies with animal models have strongly suggested that AHN does not account entirely for the beneficial effects of ADT (Bessa et al., 2008; David et al., 2009). There exists a rich literature on stress-induced neuroplasticity and depression-associated

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cellular changes that occur in other limbic brain regions, namely the orbitofrontal cortex, the anterior cingulate cortex and the amygdala (Vyas et al., 2002; Goldwater et al., 2009; Gorman and Docherty, 2010; Conrad et al., 2011; Torres-Platas et al., 2011). The recent discovery of cells in the human amygdala displaying an immature interneuron morphology and expressing the neuroplastic markers doublecortin (DCX) and polysialilated neural cell adhesion molecule (PSA-NCAM) (Zhang et al., 2009; deCampo & Fudge, 2012), has raised the intriguing possibility that adult neurogenesis may be more widespread than previously thought. This is in line with accumulating evidence of neurogenic niches in other (non-limbic) brain regions (see review in: Gould, 2007), as well as reports of a temporal migratory stream in the primate brain that might provide the amygdala and piriform cortex with new, adult-born neurons (Bernier et al., 2002). Yet more recent studies have suggested that the majority of these DCX- and PSA-NCAM-expressing cells constitute a subset of developmentally-derived interneurons (Luzzati et al., 2009; Alán et al., 2010), albeit ones that seem to display an immature phenotype. In the piriform cortex of adult rodents, DCX-IR cells with interneuronal morphology also possess electrophysiological properties similar to those of newly-generated HPC granule cells (Klempin et al., 2011; Nissant et al., 2009). DCX- and PSA-NCAM-IR neurons in the mature amygdala may therefore represent a population of cells ideally suited to respond and adapt to environmental stressors, and a source of highly plastic neurons within mature brain regions in which neurogenesis occurs at low levels, or not at all.

The purpose of the present human post-mortem study was to investigate whether the expression of proteins associated with neurogenesis and neuroplasticity is altered in the amygdala of individuals having suffered from depression. To this end, we employed immunoblotting to quantify proliferating cell nuclear antigen (PCNA), DCX, and PSA-NCAM in the basolateral amygdala (BLA) of individuals with a history of depression as well as matched psychiatrically healthy controls (CTRLs). Our working hypothesis was that individuals having suffered from depression present a global impairment in limbic brain neuroplasticity, and that this would be reflected by altered expression of neuroplastic markers in the BLA, a region highly responsive to stress (Roozendaal et al., 2009). Following this initial exploration, which unexpectedly revealed increased expression of neuroplastic markers in the BLA of depressed subjects, the latter were divided on the basis of whether they died by suicide or not. Immunoblotting of BLA and central amygdala (CeA) samples was completed for additional proteins including brain-derived neurotrophic factor (BDNF), inhibitory neuronal markers parvalbumin (PV), calbindin (CB), calretinin (CR), and glutamate decarboxylase 67 (GAD67), as well as oligodendrocyte precursor marker neuron-glia 2 (NG2) and stem cell marker Sox2.

2. Methods

2.1. Subjects

This study was conducted with the approval of the Douglas Institute Research Ethics Board and with written informed consent from next-of-kin. Fresh-frozen postmortem samples from the basolateral (BLA; $n = 36$) and central amygdala (CeA; $n = 39$) were obtained from the Quebec Suicide Brain Bank, which is part of the Douglas-Bell Canada Brain Bank (http://www.douglas.qc.ca/page/brain-bank). Samples were prepared by expert brain bank staff. In brief, dissections were performed on 0.5 cm-thick coronal sections with the guidance of a human brain atlas (Mai et al., 2007; see also http://www.thehumanbrain.info/brain/bn_brain_atlas/brain.html). BLA samples were obtained by dissecting the ventromedial third of the amygdalar tissue found in sections equivalent to plate 25 (4.0 mm from the center of the anterior commissure) of the atlas. CeA samples were obtained by dissecting the dorsal tip of the amygdala, immediately ventral to the junction between the external globus pallidus and the putamen, in sections equivalent to plate 28 (8.0 mm from the center of the anterior commissure) of the atlas.

Tissues were dissected from brains of individuals who had 6-month and/or lifetime diagnoses of major depression (D) and from individuals without any history of mood, psychotic, or neurological disorders (CTRL) (Table 1). Cause of death was ascertained by the Quebec Coroner's Office, and post-mortem psychological autopsies performed by proxy-based interviews as described previously (Dumais et al., 2005). Briefly, the Structured Clinical Interview for DSM-IV Psychiatric Disorders (SCID-I) was conducted by a trained interviewer with one or more informants of the deceased. Interviews, SCID-I assessments, case reports, Coroner's notes, and medical records were then reviewed by a panel of clinicians in order to obtain a consensus diagnosis. All suicides died

Table 1
Subject information.

	Controls		Depressed	
	BLA	CeA	BLA	CeA
n	14	14	22	25
M/F	13/1	13/1	18/4	21/4
Age (SD)	44.21 (15.34)	43.5 (16.26)	47.70 (18.28)	46.33 (16.88)
PMI (SD)	25.52 (13.04)	24.23 (13.44)	29.21 (20.44)	22.28 (20.93)
Brain pH (SD)	6.54 (0.33)	6.53 (0.34)	6.59 (0.3)	6.55 (0.27)
Alcohol/drug dependence	1/0	1/0	4/1	4/2
ADT at time of death	0	0	1	1
Suicide	0	0	12	14
Cause of Death	CVE (7)	CVE (6)	Hanging (5)	Hanging (8)
	Car accident (3)	Car accident (4)	APX (3)	APX (3)
	Cancer (3)	Cancer (3)	Jump (2)	Jump (1)
	Unknown (1)	Unknown (1)	INTOX (1)	INTOX (1)
			GSW (1)	GSW (1)
			Car accident (5)	Car accident (5)
			CVE (2)	CVE (2)
			Natural causes (2)	Natural causes (2)
			Unknown (1)	Unknown (2)

Abbreviations: ADT: antidepressant treatment; APX: asphyxiation; CVE: cardiovascular event; GSW: gunshot wound; INTOX: intoxication.