Increased Phosphorylated ERK 1/2 in Obsessive Compulsive Disorder (OCD)

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Received: February 28, 2020; Published: April 07, 2020

Abstract

Obsessive-compulsive disorder (OCD) is an anxiety disorder associated with unwanted and repeated thoughts, feelings, ideas, sensations or compulsive behaviors. The extracellular signal-regulated kinases, ERK (extracellular-signal-regulated kinase) 1 and ERK2, are central elements of one of the intracellular signaling cascades, the mitogen activated protein kinase (MAPK) pathway. Importantly, they are genetically linked to ASDs and other syndromes typified by intellectual disability. In this study, we measured phosphorylated ERK 1 and 2 in individuals with OCD and found that phosphorylated ERK is significantly increased in OCD.

Keywords: Obsessive-Compulsive Disorder (OCD); Extracellular-Signal-Regulated Kinase (ERK); Mitogen Activated Protein Kinase (MAPK)

Introduction

Obsessive-compulsive disorder (OCD) is an anxiety disorder associated with unwanted and repeated thoughts, feelings, ideas, sensations (obsessions), or compulsive behaviors [1]. Often, the obsessions are recognized as irrational or excessive, persistent and unwanted, and cannot easily be dismissed. The anxiety associated with obsessions is often perceived as incomplete or wrong or that terrible consequences will ensue if specific actions are not taken. Many patients engage in repetitive, compulsive behaviors in order to discharge the anxiety associated with obsessional thoughts [2,3]. The lifetime prevalence of OCD is estimated to be 1% to 3%, with the greatest risk in childhood and early adulthood [4-6].

The extracellular signal-regulated kinases, ERK1 and ERK2, are central elements of one of the most prominent intracellular signaling cascades, the mitogen activated protein kinase (MAPK) pathway. The ERKs play critical roles in brain development and synaptic plasticity [7] and are activated in response to a broad range of stimuli including growth factors, neurotransmitters, morphogens and transient increases in synaptic calcium [8]. Importantly, they are genetically linked to ASDs and other syndromes typified by intellectual disability [9,10] and mutations in elements of the ERK/MAPK pathway alter the activity of the ERKs, resulting in a group of genetic disorders collectively known as “RASopathies”. These syndromes are typified by intellectual disabilities, developmental and language deficits, ASD, and psychiatric disease [11,12].

Citation: AJ Russo., et al. “Increased Phosphorylated ERK 1/2 in Obsessive Compulsive Disorder (OCD)”. EC Neurology 12.5 (2020): 07-10.
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**Material and Methods**

Cellular phosphorylated ERK 1 and 2 concentrations was measured in 11 individuals with diagnosed OCD and 10 age and gender similar neurotypical, controls.

White blood cells from consecutive individuals with diagnosed OCD (n = 11; 7 male; mean age 36 years) and controls (n = 10; 7 male; mean age 39 years) were obtained from patients presenting at the Health Research Institute (HRI)* over a two year period. All OCD individuals who presented to HRI were asked to participate, and patients who participated in this study were randomly chosen from all patients who volunteered. Neurotypical control plasma was obtained from HRI and randomly chosen from a selection of about 200 samples. Patient consent was obtained from all patients involved in this study and this study was approved by the IRB of the HRI.

**Cellular phosphorylated ERK 1 and 2 concentrations was measured using an ELISA**

1. 50 μL/well of 1X Cell Lysis Mix (negative control) and 50 μL/well Positive Control Cell Lysate (positive control) to separate assay wells for controls.

2. 40 μl of lysis buffer (contains a combination of detergents, phosphatase inhibitors, salts and buffers) was added to each of the control and experimental wells.

3. 10 μl of buffy coat cells (experimental and controls) were added to appropriate wells and mixed gently.

4. 50 μL/well of Antibody Cocktail mix (detection antibody and HRP conjugated antibody) was added to all the assay test wells. The plate was incubated for 1 hr at room temperature on a microplate shaker (~ 300 rpm).

5. Wells were washed with 300 μL/well 1X Wash Buffer 4 times.

6. 100 μL of Detection Reagent (TMB) was added to each well and the wells were incubated for 10 - 30 minutes.

7. After colour development, 100 μL of Stop Solution was added to each well.

8. Absorbance was measured using a colorimetric (spectrophotometric) plate reader (BioRad) set at 450 nm.

**Buffy coat white blood cells**

All experimental and control cells were separated from whole blood using centrifugation and were treated in an identical fashion refrigerated (4°C) immediately after collection and cell/serum separation, then used within 4 hours ERK concentration determination or cells were frozen at -7°C and used for ELISAs within 6 months of retrieval.

**Statistics**

Inferential statistics were derived from t-test with 95% confidence intervals.

**Results**

We used an ELISA to measure ERK 1 and 2 in individuals with OCD (N = 11) and age and gender similar neurotypical controls (N = 10). We found ERK levels to be significantly increased in these individuals compared to controls (p = 0.04) (Figure 1).

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Discussion

There is support for the relationship between ERK and the etiology of OCD. OCD-like behavior in SPRED2 knockout (KO) mice, has been alleviated by treatment with the selective serotonin reuptake inhibitor fluoxetine. Also, electrophysiological measurements revealed altered transmission at thalamo-amygdala synapses and morphological differences in lateral amygdala neurons of SPRED2 KO mice where fear memories are thought to be stored [13].

Changes in synaptic function were accompanied by dysregulated expression of various pre- and postsynaptic proteins in the amygdala in SPRED2 mice. This was a result of altered gene transcription and triggered upstream by upregulated tropomyosin receptor kinase B (TrkB)/ERK-MAPK signaling in the amygdala of SPRED2 KO mice. The MEK inhibitor selumetinib, suppressed TrkB/ERK-MAPK pathway activity in vivo and reduced OCD-like grooming in these SPRED2 KO mice [13]. This suggests that upregulation of the Ras/ERK-MAPK pathway is involved in the development of OCD-related disorders.

Conclusion

Our results also suggest that the MAPK pathway is upregulated in OCD as ERK levels are increased in OCD individuals. This suggests that therapies, such as MAPK inhibitors [14] designed to normalize ERK levels, may be successful in improving OCD behaviors.

Competing Interests

The authors have no competing interests.

Acknowledgements

The author would like to acknowledge the financial support from the Autism Research Institute.

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Volume 12 Issue 5 May 2020
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