INTRODUCTION

Do Drugs that Carry a Black Box Warning for Suicidal Ideation Activate a Common Neural Circuit in the Brain?

Hypothesis

Drugs for risk of suicide share a common distributed neural circuit involved with cognitive function.

Approach

Use pMRI to identify brain activity common to all drugs with black box warnings for suicide. Screen this library against drugs used to treat suicidal and aggressive behaviors. Use mutually exclusive brain areas as the “finger print” of a putative neural circuit involved in suicidal ideation and self-injury.

Choice of Drugs at Risk

Black Box Warnings

Venlafaxine – used to treat depression. Functions as a serotonin-norepinephrine reuptake inhibitor.

Rilmenabant – used to treat obesity. Functions as an inverse agonist for the cannabinoid receptor CB1.

Gabapentin – used to treat epilepsy and neuropathic pain. Functions as a GABA analogue acting on voltage-dependent calcium channels.

Choice of Control Drugs

Clozapine – used to treat schizophrenia. Functions as an atypical antipsychotic acting on multiple signaling systems. FDA approved for the treatment of suicide risk in schizophrenics.

Buspirone – used primarily to treat anxiety. Also indicated for treatment of aggression associated with head injury. Functions as serotonin 5-HT1A partial agonist.

MATERIALS AND METHODS

Imaging Technology

Studies were performed with a quad transmit/receive head coil and rat restrainer developed by Ekam Imaging Technologies, (Lexington, MA).

Experimental Design

• Male, Long Evans rats (ca. 350 g body weight)
• Acclimate to imaging procedure and head restraint
• On the Day of Imaging (within one week of acclimation)
• Positioned in animal restrainer under 2% isoflurane
• Allowed to awaken - 6 min anatomical scan
• 35 min function scan (spin echo EPI):
  5 min control
  30 min post tail vein injection of drug

Methodological Approach to Screening Drugs at Risk for Suicide

Tool: Pharmacological MRI in Awake Rats

Pattern of brain activity following drug administration (graphic representation)

Data Base of Drugs Used for the Treatment of Suicide and Aggression

Drug A Drug B Drug C Drug D Drug E

Pattern of brain activity following drug administration (graphic representation)

Common Brain Activity

Statistical analysis testing for similarity between BOLD signal changes in 154 different brain areas revealed a difference in neural activity between drugs F & G and the common brain activity found in Drugs A-E.

Summary

Pharmacological MRI comparing BOLD signal changes across 154 brain areas revealed a difference in neural activity between drugs at risk for suicide and those used to treat suicidal ideation and aggression. The brain areas comprising this putative neural circuit characteristic of drugs at risk for suicide include:

- prelimbic cortex;
- gustatory cortex; insular cortex
- secondary somatosensory cortex; parietal cortex
- medial dorsal striatum
- anterior thalamus; ventral anterior lateral thalamus
- reuniens thalamus; ventral medial thalamus
- lateral posterior thalamus; lateral dorsal thalamus
- central thalamus
- CA1 hippocampus
- posterior hypothalamus
- central raphe

Limitations and Considerations

• The present Data Base for Risk is limited to three drugs and requires several more candidates.
• Without an extensive Data Base there is a greater likelihood of classifying drugs as false negatives or positives.
• Choice of drugs for the Control Data Base – at present limited to clozapine and buspirone. Would it make sense to include any psychotherapeutic drugs without a Black Box Warning for suicide?
• These patterns in brain activity do not reflect a behavioral phenotype, i.e. rats do not display suicidal behavior. Identifying a circuit in rats does not imply that there is a “suicide” circuit in humans.
• The hypothesized involvement of brain areas associated with executive function and working memory in humans would be better studied in non-human primates than rodents.