Females

Antidepressant Regulation of Macrophage-derived TNF Production

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Abstract

The role of the cytokine tumor necrosis factor-α (TNF) has been well established in neurogenic pain and depression, two often comorbid conditions that are associated with chronic inflammation. Antidepressant drugs have been found to be effective in treating these conditions and in reducing brain-derived TNF, but the effect of these drugs elsewhere in the body is poorly characterized. This study seeks to determine the effects of antidepressant drugs on macrophage-derived TNF production and elucidate whether the macrophage inflammatory state influences these effects. This was studied using peritoneal macrophages isolated from Sprague-Dawley rats that were exposed to various concentrations of different classes of antidepressants, with inflammation simulated using lipopolysaccharide. It was found that antidepressants regulate macrophage-derived TNF production in a gender, inflammation, and dose dependent manner. These findings can have implications in elucidating an additional mechanism of antidepressant action and determining pharmacological differences between genders.

Introduction

- Tumor necrosis factor-α (TNF) is a pro-inflammatory cytokine that can be produced by a variety of different cell types.
- Macrophages (MΦ), a type of resident phagocyte, are modulated by many neurotransmitters and neuropeptides.
  - Norepinephrine (NE) - MΦs express both α2 (promote TNF) and β-adrenergic (inhibit TNF) receptors.1-3
  - Serotonin – associated with suppression of TNF production.3
  - Dopamine – high extracellular concentrations suppress TNF production.3
- One mechanism of action of antidepressants is inhibition of reuptake mechanisms. This blockade prevents removal of neurotransmitters from extracellular space, prolonging the response to the corresponding neurotransmitter.
- Antidepressants have been found to have anti-inflammatory effects, which supports their use in depression and neuropathic pain, two conditions associated with chronic inflammation.4-7
- The link between antidepressant drugs and decrease in brain TNF has been established2, along with modulation of the immune response.10

Methods and Materials

- Male and female Sprague-Dawley rats (125-150 g, Envigo) were housed in the UB-Laboratory Animal Facilities.
- Animals were given food and water ad libitum and maintained on a 12 hour light/dark cycle.
- Peritoneal exudate cells were collected immediately after decapitation via peritoneal lavage and MΦs isolated via adhesion (2 hrs at 37°C, 95%O2/5%CO2).
- MΦs were exposed to antidepressants (desipramine, amitriptyline, bupropion) at 10-7M, 10-5M, and 10-3M.
- Inflammation was simulated in vitro by the addition of lipopolysaccharide (LPS, 30 ng/mL). Incomplete RPMI-1640 with glutamine was used for all incubations, drug, and LPS dilutions.
- Cell supernatants were collected after 4 hr-incubation with appropriate drugs and LPS.
- TNF levels were assessed with a spectrophotometric WEHI 164 clone 13 fibroblast cytotoxicity assay. (inhibit TNF) receptors.1-3

Results

- Percent changes were calculated by comparing TNF levels of each sample with either a no LPS group (for non-inflammatory state) or an LPS only group (for inflammatory state).
- Male rat MΦs demonstrated a flipped response to antidepressants between non-inflammatory and inflammatory states. The relationship between inflammatory state and antidepressant response was not as clear in female rat MΦs.

Discussion

- The influence of antidepressants on MΦ-derived TNF production was found to be regulated differently depending on gender, inflammatory state, and drug concentration.
- These findings suggest an additional mechanism of action of antidepressant drugs. These drugs are used in both depression and neuropathic pain, both of which are connected to an enhanced systemic inflammatory state.
- The differential regulation based on inflammatory state may also suggest a possible unintended effect of antidepressant treatment: the inhibition of inflammation in non-inflammatory environments.
- The gender differences may be due to the pharmacological differences between the genders, an important concept in drug design and testing.

Purpose

A gap in the literature exists for assessing the direct effect of antidepressants on MΦ production of TNF. This study will analyze the in vitro effects of several antidepressant drugs on MΦ-derived TNF production.

Future Experiments

- A larger number of animals will be tested to perform statistical analysis of the data.
- The in vivo model of inflammation with LPS will be supported through the use of an in vivo model of systemic inflammation by using the Chronic Inflammation Model of neuropathic pain in addition to LPS.
- A fourth group of antidepressants, the selective serotonin reuptake inhibitors, will be tested.

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References

11. Elyea Lauren Olson. A mechanism of antidepressant action is associated with decreasing levels of tumor necrosis factor (TNF) in the brain. University at Buffalo, 2014.