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Paraquat and psychological stressor interactions as pertains to Parkinsonian co-morbidity

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ABSTRACT

A number of epidemiological and experimental studies have implicated the non-selective herbicide, paraquat, in the development of sporadic Parkinson's disease (PD). While preclinical research has focused mainly on elucidating the nigrostriatal effects of paraquat, relatively little data are available concerning non-motor brain systems and inflammatory immune processes (which have been implicated in PD). Hence, in the present study, we sought to take a multi-system approach to characterize the influence of paraquat upon extra-nigrostriatal brain regions, as well ascertain whether the impact of the pesticide might be enhanced in the context of chronic intermittent stressor exposure. Our findings support the contention that paraquat itself acted as a systemic stressor, with the pesticide increasing plasma corticosterone, as well as altering neurochemical activity in the locus coeruleus, paraventricular nucleus of the hypothalamus, nucleus accumbens, dorsal striatum, and central amygdala. However, with the important exception striatal dopamine turnover, the stressor treatment did not further augment these effects. Additionally, paraquat altered inter-cytokine correlations and, to a lesser extent, circulating cytokine levels, and concomitant stress exposure modulated some of these effects. Finally, paraquat provoked significant (albeit modest) reductions of sucrose preference and weight gain, hinting at possible anhendonic-like or sickness responses. These data suggest that, in addition to being a well known oxidative stress generator, paraquat can act as a systemic stressor affecting hormonal and neurochemical activity, but largely not interacting with a concomitant stressor regimen.

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1. Introduction

Epidemiological data have for some time now supported a link between Parkinson's disease (PD) and cumulative lifetime pesticide exposure (Tanner et al., 2011; Wang et al., 2011; Kamel et al., 2013), and it has been suggested that the pro-oxidant pesticide, paraquat, could be especially relevant for some of the neuropsychiatric symptoms of the disease (Kim et al., 2013). Besides its effect on the nigrostriatal system, exposure to paraquat in rodents has produced other neurotoxic biological characteristics associated with PD including microglia activation, Lewy-body like aggregates containing α-synuclein, pro-inflammatory cytokine expression, and oxidative stress via mitochondria complex inhibition or microglia activation (Litteljohn et al., 2011a; Baltazar et al., 2014).

Upon entry into the brain, paraquat is distributed across areas including the prefrontal cortex, hippocampus, olfactory bulbs, and the substantia nigra pars compacta (SNc) (Peng et al., 2007). The pesticide was also found to induce several PD-like non-motor behavioural deficits, including olfactory dysfunction (Czerniczyniec et al., 2011), anxiety-like symptoms (Litteljohn et al., 2009; Czerniczyniec et al., 2011; Campos et al., 2013), and memory impairment (Chen et al., 2010). Nonetheless, it has yet to be determined whether paraquat can induce anhedonic-like behaviour in rodents, and the need for understanding the pesticide's

Abbreviations: 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, serotonin; ANOVA, analysis of variance; CIS, chronic intermittent immobilization/social defeat stressor; DA, dopamine; DOPAC, 3,4-Dihydroxyphenylacetic acid; EDTA, ethylenediaminetetraacetic acid; GM-CSF, granulocyte-macrophage colony-stimulating factor; HPLC, high-performance liquid chromatography; HVA, homovanillic acid; IFN-γ, interferon-γ; IL, interleukin; KO, knockout; LC, locus coeruleus; LLOQ, lower limit of quantification; MCP, monocyte chemoatrractant protein; MHPG, 3-methoxy-4-hydroexyphenylglycol; MIP, macrophage inflammatory protein; NE, norepinephrine; PD, Parkinson's disease; PVN, paraventricular nucleus; TNF-α, tumour necrosis factor-alpha.

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effects on extra-nigrostriatal brain regions should be broadened.

In addition to biological insults, it is conceivable that psychologically relevant stressors could affect the primary motor symptoms and neurodegenerative process (Urakami et al., 1988; Metz, 2007; Kibel and Drenjancević-Perić, 2008; Smith et al., 2008), as well as non-motor or co-morbid neuropsychiatric manifestations in PD patients. For instance, major life events influenced the development of depression among PD patients (Rod et al., 2013), and psychological therapies have proven to be effective in reducing depression and anxiety symptoms in PD patients (Yang et al., 2012; Schrag et al., 2001; Hurt et al., 2012; Whitworth et al., 2013).

In the present investigation we sought to assess the individual and combined effects of the PD-linked pesticide, paraquat, and a psychologically relevant chronic intermittent immobilization/social defeat stressor (CIS) challenge. We were particularly interested in further characterizing the influence of paraquat upon extra-nigrostriatal brain regions and ascertaining whether the disparate classes of stressors (chemical vs. psychological) would interact to influence hedonic behaviour. It was also of interest to determine whether any such effects would be accompanied by changes in stressor hormone levels (corticosterone), central neurotransmitter activity and immune messengers (circulating cytokines). Specifically, it was hypothesized that chronic systemic paraquat administration and concurrent CIS exposure would provoke physiological and behavioural changes consistent with a depressive-like phenotype, as expected in a sizable portion of PD patients.

2. Materials and methods

2.1. Animals and general experimental design

Male C57BL6/J mice were obtained at 6–7 weeks of age from The Jackson Laboratory (Bar Harbor, ME, USA) and acclimated to our vivarium for 2 weeks. Animals were singly housed in standard polypropylene cages (27 × 21 × 14 cm) and maintained on a 12-h light/dark cycle with lights on at 08:00 h. A diet of Ralston Purina (St. Louis, MO) mouse chow and water was provided ad libitum, and room temperature was maintained at ~21 °C. One week prior to the commencement of the study, mice were randomly assigned to one of four experimental conditions (No stress/Saline; No stress/Paraquat; Stress/Saline; Stress/Paraquat) and sucrose preference training initiated (n = 10–12). A further 8 mice comprised the testing-naïve negative control: except for behavioural testing (see below), these animals received identical treatment to the No stress/Saline mice. All animals were rapidly decapitated 2 h following the final paraquat or saline injection. In order to minimize the effects of diurnal variations, tests and procedures were carried out between the hours of 08:00 and 13:00. All experimental procedures were approved by the Carleton University Committee for Animal Care and complied with the guidelines set out by the Canadian Council for the Use and Care of Animals in Research.

2.2. Experimental treatments: paraquat and chronic intermittent stress

All mice received intraperitoneal injection with 10 mg/kg paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride; Sigma Aldrich, St Louis, MO, USA) or physiological saline (Sigma Aldrich). Injections were administered twice a week for 6½ weeks (13 injections in total) on a regular interval basis. This paraquat dose is routinely used in our lab and has been shown to reliably induce nigrostriatal damage (~25–35% neuron loss) (Mangano and Hayley, 2009; Mangano et al., 2011). During the 30 min immediately preceding each injection, half of the animals were either socially defeated or physically restrained in semicircular Plexiglas tubes (4 × 12 cm) with tails taped to prevent turning. The social defeat paradigm involved introducing experimental mice into the home-cage of a significantly larger and more aggressive mouse (retired CD1 breeders from Charles River, QC, CAN). A mesh wire divider was inserted into the cage upon the first display of submissive behaviour (upright posture with belly exposed) or if excessive fighting occurred (continuous biting); this had the effect of physically separating the mice while still allowing for interactions between them (Audet et al., 2011). Stressor application followed a fixed alternating schedule such that each mouse in the stressor groups received one session per week of restraint and one of social defeat. On the day of sacrifice all animals in the stressor conditions received 30 min restraint immediately prior to the final paraquat or saline injection. Due to the nature of the stressor paradigm, the stressed animals were housed in holding rooms separate from, but otherwise identical to, their non-stressed counterparts.

2.3. Brain dissection technique

Following rapid decapitation, brains were excised and sectioned into sequential coronal slices using razor blades and a chilled stainless steel microdissecting matrix with adjacent slots spaced ~0.5 mm apart. Hollow biopsy needles were used to collect the dorsal striatum, paraventricular nucleus of the hypothalamus (PVN), locus coruleus (LC) and nucleus accumbens. All tissue samples were taken with reference to the mouse brain atlas of Franklin and Paxinos (1997). Samples were maintained in a homogenizing solution containing 14.17 g monochloroacetic acid, 0.0186 g disodium ethylenediamine tetraacetate (EDTA), 5.0 ml methanol, and 500 ml H_2O; and stored at −80 °C until determination of central monoamine and metabolite levels using high performance liquid chromatography (HPLC).

2.4. Plasma corticosterone assay

At the time of decapitation, trunk blood from all of the animals, including those in the behavioural testing-naive control group, was collected in tubes containing 10 μg EDTA. Samples were centrifuged (3000g for 8 min) and the plasma removed and stored in aliquots at −80 °C for later corticosterone determination with commercially available radioimmunoassay kits (ICN Biomedicals, CA, USA). Samples were assayed in duplicate within a single run to control for inter-assay variability; the intra-assay variability was less than 10%. Separate plasma aliquots were used for the cytokine determinations.

2.5. Plasma cytokine quantification

Circulating levels of 11 different cytokines were determined by multiplex analysis using the Luminex 100 suspension-based bead array system (Luminex Corp., Austin, TX) and a custom multiple cytokine detection kit (MILLIPLEX MAP Mouse Cytokine/Chemokine Kit, Millipore, Cat. #MPXMCYTO-70K). Each of the 11 cytokines assayed are listed in Table 1. The assay was performed according to the kit manufacturer's instructions (see www.millipore.com/userguides) and, unless otherwise indicated, all reagents were provided in the multiplex kit. Eight samples from each of the four treatment groups were run in duplicate; the remaining samples were singly run. Where applicable, results of duplicate sample determinations were averaged prior to the data being analysed. In cases where cytokine levels were so low as to be undetectable, samples were assigned a value of one-half the lower limit of quantitation.

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