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Research report

The long-term impact of oxaliplatin chemotherapy on rodent cognition and peripheral neuropathy

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HIGHLIGHTS

- Oxaliplatin caused peripheral neuropathy shortly after treatment, but had resolved by 1 month.
- Oxaliplatin caused impairment in object and location recognition.
- Oxaliplatin induced cognitive impairment persisted for 11 months after treatment.
- Higher doses of oxaliplatin resulted in worse peripheral neuropathy and cognitive impairment.

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ABSTRACT

Chemotherapy treatment is associated with cognitive dysfunction in cancer survivors after treatment completion. The duration of these impairments is unclear. Therefore this paper aims to evaluate the lasting impact of varying doses of the chemotherapy oxaliplatin (OX) on cognition and peripheral neuropathy. In Experiment 1 rats were treated once a week for 3 weeks with either physiological saline (control) or 6 mg/kg OX i.p. and were assessed for peripheral neuropathy, using von Frey filaments, and cognitive function, using novel object and location recognition, up to 2 weeks after treatment completion. For Experiment 2 rats received 3 weekly i.p. injections of either physiological saline (control), 0.6 mg/kg, 2 mg/kg or 6 mg/kg OX and assessed for peripheral neuropathy and cognitive function up to 11 months after treatment completion. Systemic OX treatment induced lasting effects on cognitive function at 11 months after treatment, and peripheral neuropathy at 1 month after treatment and these were dose dependent; higher doses of OX resulted in worse cognitive outcomes and more severe peripheral neuropathy.

1. Introduction

Research suggests that systemic chemotherapy for the treatment of cancer is associated with subtle impairment across a range of cognitive domains [1]. Patients report noticeable difficulties with memory and attention [2], and traditional neuropsychological testing consistently finds the domains of verbal and visual memory, attention and processing speed and executive function to be impaired after chemotherapy [e.g. 3]. What is not clear from this work is whether changes in cognitive function after chemotherapy are transient or sustained. Cross-sectional studies have found cognitive impairment lasting between 2 and 10 years post chemotherapy [3–5]. Longitudinal prospective studies have shown that a subset of survivors experience cognitive difficulties in the first few months after treatment completion [6], and this can persist for up to 1–2 years after chemotherapy completion [7,8].

Preclinically a number of studies using rodent models of cognition suggest that systemic treatment with chemotherapy agents such as methotrexate, 5-fluorouracil (5-FU), cyclophosphamide and doxorubicin, is associated with cognitive dysfunction within a few weeks of treatment completion [9–15]. However, there have been inconsistent findings amongst the few studies that have examined rodent cognitive function several months post treatment. Some research suggests that chemotherapy is associated

Abbreviations: CNS, Central nervous system; OX, Oxaliplatin; NOR, Novel object recognition; NLR, Novel location recognition; 5-FU, 5-fluorouracil.

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with long-lasting cognitive impairment; Li et al. [16] found rats treated with cytosine arabinoside had impaired remote spatial reference memory when tested 1 month after treatment, and Mondie et al. [17] found mice treated with thioTEPA had impaired object recognition 5 months after treatment. However, others have failed to find lasting impairments due to single agent treatment with 5-FU or doxorubicin alone [18]; or combined treatment with cyclophosphamide and doxorubicin [18] or cyclophosphamide and 5-FU [19,20].

Little work has been done to evaluate the impact of treatment with platinating agents on cognitive function, despite their widespread clinical use. There is evidence to suggest that testicular cancer survivors treated with chemotherapy regimens containing a platinum agent, typically cisplatin, experience cognitive dysfunction after treatment completion [21–23]. Preclinically, Song et al. [24] found mice treated with cisplatin had impaired performance on active and passive avoidance tests of learning and memory. This was associated with increases in markers of oxidative stress. Although cognition was not evaluated, Dietrich et al. [25] found increased cell death and decreased neural and oligodendrocyte proliferation in mice treated with clinically equivalent doses of cisplatin.

Oxaliplatin (OX) is a cisplatin analogue commonly used in the treatment of adjuvant and metastatic colorectal cancer [26]. It is thought to have multiple mechanisms of action against cancer cells including: the formation of DNA lesions via the creation of crosslinks, cell cycle arrest and inhibition of messenger RNA synthesis [27]. OX is associated with the occurrence of peripheral neuropathy. This dose-limiting toxicity is extremely common and occurs in both an acute and chronic form. The acute form typically appears shortly after treatment and tends to disappear after a few days [28], and is associated with changes in voltage-gated sodium channels [27]. In contrast, the chronic form occurs in patients who have received a cumulative dose of more than 800 mg/m^2 and appears to be associated with accumulation of platinum in the dorsal root ganglia [27,29]. OX treatment similarly causes peripheral neuropathy in rodents [30]. Our laboratory has previously demonstrated systemic OX treatment is associated with short term cognitive impairment in rodents [31,32]. These studies found a single dose of 12 mg/kg OX induced impairments in novel object recognition 10 days later [32] and renewal of contextual fear by 16 days [31]. However, the long term effects of OX treatment on cognitive function are yet to be investigated.

Therefore, the aims were to firstly investigate in rodents the impact OX treatment has on cognitive function and peripheral neuropathy in the same animals, and secondly to evaluate the duration of cognitive impairment and peripheral neuropathy.

2. Methods

2.1. Subjects

Upon arrival, healthy male hooded Wistar rats (Lab animal services, Adelaide University) were housed in groups of 4–6 in large acrylic tubs with continuous access to food and water and allowed to acclimatise to the facility for 7 days prior to experimentation. The homecages were kept in a colony room with a 12:12 h light:dark cycle, lights on at 0800 h, maintained at 21 °C ±1 °C. Rats were weighed daily during experimentation and monitored daily during treatment and at least 7 days after for signs of toxicity including dehydration, piloerection, pica, difficulties in breathing, gait and signs of postural abnormalities. All experimentation was approved by the Animal Ethics Committee at the University of Sydney.

2.2. Drug administration

Oxaliplatin (OX; Spirit Pharmaceuticals, Australia) was prepared according to the manufacture's instructions to a dilution of 5 mg/ml in 5% dextrose solution. For Experiment 1, rats received 3 X weekly intraperitoneal (i.p.) injections of either physiological saline (control, $n = 12$), or 6 mg/kg OX ($n = 14$). For Experiment 2, rats received 3 X weekly i.p. injections of either physiological saline (control, $n = 10$), 0.6 mg/kg ($n = 10$), 2 mg/kg ($n = 10$) or 6 mg/kg OX ($n = 9$). Rats were counterbalanced prior to treatment so that there were no between group differences according to weight ($Fs < 1$, $p > .05$).

2.3. Procedure

2.3.1. Experiment 1

Mechanical sensitivity was assessed prior to the commencement of treatment and during treatment at 24 h, and every second day thereafter for the first week. Rats were again assessed for changes in mechanical sensitivity at the end of behavioural testing (i.e. 24 days after treatment completion). Behavioural testing commenced 1 week after treatment completion. Novel object recognition (NOR) was conducted after habituation on day 10 post treatment, and novel location recognition (NLR) was assessed 6 days later (i.e.16 days after treatment completion).

2.3.2. Experiment 2

Mechanical sensitivity was assessed prior to treatment, weekly during treatment and at 1 week, 2 weeks, 1, 4, 6 and 11 months post treatment completion. NOR was assessed at 1 week, 1, 4, 6 and 11 months post treatment. OLR testing took place at 2 weeks, 1, 4, 6 and 11 months post treatment. At the 1, 4, 6 and 11 month tests, location recognition was assessed 48 h after object recognition testing was completed.

2.4. Behavioural testing

2.4.1. Mechanical sensitivity

Rats were tested for mechanical sensitivity with von Frey filaments using a procedure previously described [33]. Prior to testing, rats were habituated for 45 min to sitting on an elevated metal rod flooring. The rods were spaced 2 cm apart, to allow the filaments to be passed. Testing was performed using 0.406–15.136 gm calibrated Semmes-Weinstein monofilaments (von Frey hairs; Stoelting, Wood Dale, IL). During testing the filaments were applied to each hind-paw twice for 8s, alternating between left and right hind-paws. Whether the rat withdrew its paw or not was recorded, and testing proceeded until two consecutive withdrawals were made to the same weight filament on each foot. The inter-trial interval was approximately 5 min, such that 10 min elapsed before reapplication of the filament to the same foot.

2.4.2. Novel object recognition (NOR) and novel location recognition (NLR)

The rat's ability to recognize familiar and novel objects was assessed using NOR, and spatial location recognition using NLR [34–36]. For both recognition memory tasks, prior to testing animals were habituated to the black circular test arena (80 cm diameter × 30 cm high) in the absence of any objects. The following day the rats completed both a sample and test trial. During the sample trial two identical objects were presented, placed 30 cm apart, and rats were given 3 min to freely explore the objects. For NOR, after sample trial completion, the rat was returned to its home cage for 2 h. This was followed by a 3 min test trial, during which the rat explored a replica of the familiar object and a novel object. The novel and familiar objects differed in both texture and size. For NLR, the rats were returned to their homecage for 15 min before a