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The chemotherapeutic agent paclitaxel selectively impairs reversal learning while sparing prior learning, new learning and episodic memory

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ABSTRACT

Chemotherapy is widely used to treat patients with systemic cancer. The efficacy of cancer therapies is frequently undermined by adverse side effects that have a negative impact on the quality of life of cancer survivors. Cancer patients who receive chemotherapy often experience chemotherapy-induced cognitive impairment across a variety of domains including memory, learning, and attention. In the current study, the impact of paclitaxel, a taxane derived chemotherapeutic agent, on episodic memory, prior learning, new learning, and reversal learning were evaluated in rats. Neurogenesis was quantified post-treatment in the dentate gyrus of the same rats using immunostaining for 5-Bromo-2′-deoxyuridine (BrdU) and Ki67. Paclitaxel treatment selectively impaired reversal learning while sparing episodic memory, prior learning, and new learning. Furthermore, paclitaxel-treated rats showed decreases in markers of hippocampal cell proliferation, as measured by markers of cell proliferation assessed using immunostaining for Ki67 and BrdU. This work highlights the importance of using multiple measures of learning and memory to identify the pattern of impaired and spared aspects of chemotherapy-induced cognitive impairment.

1. Introduction

Paclitaxel is a chemotherapeutic drug from the taxane family commonly used to treat lung, pancreatic, ovarian and breast cancers. Chemotherapeutic agents produce anti-tumor effects by blocking or suppressing proliferation of dividing cells. Paclitaxel binds to the beta subunit of tubulin which then results in the polymerization of microtubules, thereby producing apoptosis. However, the efficacy of this cancer therapy is undermined by adverse side effects including peripheral neuropathy and cognitive impairment. Taxane chemotherapeutic agents induce peripheral neuropathy characterized by sensory abnormalities including tingling, numbness, as well as shooting and burning pain (Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008); these sensory abnormalities are observed in both humans and non-human animals alike (Cavaletti, Alberti, Frigeni, Piatti, & Susani, 2011; Deng et al., 2012; Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010; Polomano, Mannes, Clark, & Bennett, 2001; Rahn et al., 2008; Wolf et al., 2008). Peripheral neuropathy can occur early in chemotherapy treatment and persist long after treatment cessation (Authier et al., 2009) and is reported to occur in approximately 30–40% of patients. Consequently, clinicians are forced to weigh the potential for therapeutic efficacy of dosing and administration schedule against the potential of inducing a painful state of peripheral neuropathy in patients. Reduction in cognitive function following anti-cancer treatment, referred to as chemotherapy-induced cognitive impairment (CICI) or "chemo-brain" among patient groups, is another debilitating side effect of chemotherapeutic treatment. Adverse cognitive side effects include difficulty sustaining attention, poor concentration, slower processing speed, and poor learning and memory (Ahles & Saykin, 2002; Wefel & Schagen, 2012). Up to 70% of cancer survivors report cognitive deficits during and after chemotherapy treatment (Ahles & Saykin, 2007; Seigers & Fardell, 2011). CICI symptom onset occurs as early as 5 h post-treatment and lasts up to 6 months after administration or longer (Schultz, Beck, Stava, & Vassilopoulou-Sellin, 2003). Patients treated with combination chemotherapy including paclitaxel have impairments of cognitive functioning (Ahles & Saykin, 2002; Wefel & Schagen,

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2012). Specifically, patients receiving a combination of paclitaxel, 5-fluorouracik, cyclophosphamide and adriamycin showed deficits in learning and memory for up to a year following treatment (Ahles & Saykin, 2002). Furthermore, not all cancer survivors report a full CICI recovery following treatment cessation. Thus, despite paclitaxel's low CNS penetration rate, taxane chemotherapeutic agents have a detrimental impact on cognitive functioning that have deleterious effects on patients' quality of life. To date, no treatment for CICI has been recognized (Belzung, Wigmore, & ebrary Inc., 2013) and a greater understanding of the underlying causes and mechanisms is critical if novel therapeutics that improve quality of life in survivors are to be developed for clinical use.

The mechanisms behind adverse side effects of chemotherapy on cognition remain poorly understood. Blood-brain penetration of chemotherapy drugs may affect brain structure and function (Belzung & Wigmore, 2013). Decreased cell proliferation in the hippocampus is also postulated to underlie chemotherapy-induced cognitive dysfunction (Briones & Woods, 2011; Winocur, Wojtowicz, Huang, & Tannock, 2014). A change in the level of hippocampal neurogenesis is a key biological mechanism proposed to underlie CICI. The hippocampus has been implicated in learning, memory, and spatial processing (Eichenbaum, 2000; Eichenbaum, 2007; Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Eichenbaum, Yonelinas, & Ranganath, 2007; Ergorul & Eichenbaum, 2004; Gold, Hopkins, & Squire, 2006; Kim, Dede, Hopkins, & Squire, 2015; Shrager, Bayley, Bontempi, Hopkins, & Squire, 2007; Smith, Wixted, & Squire, 2011) and has been shown to exhibit neurogenesis in adulthood (Zhao, Deng, & Gage, 2008). In the adult mammalian brain, neurogenesis occurs in the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus.

Throughout this process, new dentate granule cells get integrated into existing hippocampal circuits, some of which are thought to be critical for memory (Deng, Aimone, & Gage, 2010). These newborn neurons have been shown to play a role in hippocampal function by assessing diverse hippocampal-dependent behaviors (Kee, Teixeira, Wang, & Frankland, 2007; Ramirez-Amaya, Marrone, Gage, Worley, & Barnes, 2006; Tashiro, Makino, & Gage, 2007). Adult born dentate granule cells undergo preferential recruitment into hippocampal neural circuits that mediate novelty recognition, associative learning, and spatial memory (Denny, Burghardt, Schachter, Hen, & Drew, 2012; Kee et al., 2007; Ramirez-Amaya et al., 2006). Decreased neurogenesis also accompanies deleterious effects in some forms of hippocampal-dependent learning and memory (Arruda-Carvalho, Sakaguchi, Akers, Josselyn, & Frankland, 2011; Drew, Denny, & Hen, 2010). Together, these findings suggest that hippocampal neurogenesis plays a critical role in hippocampal-dependent domains of cognition. Chemotherapy drugs suppress cell proliferation, including newly generated hippocampal neurons in both human and animal models (Pereira Dias et al., 2014; Winocur, Wojtowicz, & Tannock, 2015). Decreased hippocampal neurogenesis has been documented following treatment with multiple chemotherapy drugs both individually (Janelsins et al., 2010) and when treated in combination (Briones & Woods, 2011; Christie et al., 2012; Winocur et al., 2015) and may accompany CICI induced by paclitaxel.

Despite the wide range of symptoms observed in human patients, only a limited range of behavioral tasks have been used to evaluate cognitive impairments attributed to chemotherapeutic treatment in rodents. To date, measures of chemotherapy-induced cognitive deficits in rodents have predominantly focused on hippocampal and frontal dependent functions including spatial navigation (Morris Water maze), novelty recognition (novel location recognition), associative learning and memory (non-match to sample and delayed non-match to sample). Chemotherapy impaired spatial memory, conditional associative learning, and discrimination learning (some of which were chronically observed (Winocur et al., 2012)), and it suppressed hippocampal neurogenesis (Winocur et al., 2015).

Another domain of cognitive function relevant to memory is that of episodic memory. Episodic memory is described as the memory for unique personal past events. Elements of episodic memory include memory for what, where, and when a specific event occurred. Episodic memory encodes the origin (i.e., source) of previously encountered information (Crystal, 2016; Crystal, Alford, Zhou, & Hohmann, 2013; Johnson, 2005). Because source memory includes features that were present when the specific memory was encoded, it allows us to differentiate one episodic memory from another (Crystal & Smith, 2014; Johnson, Hashtroudi, & Lindsay, 1993; Mitchell & Johnson, 2009). While chemotherapy-induced episodic memory impairment has been reported in humans (Monje & Dietrich, 2012), this has been difficult to evaluate in animal models.

Animal models of source memory have documented that rats remember the source of encoded information (Crystal & Alford, 2014; Crystal & Smith, 2014; Crystal et al., 2013). In this approach, rats are asked to forage for distinctive flavors of food in a radial maze. Rats are able to remember what, where, and how they encountered distinct flavors using source memory (Crystal, 2016; Crystal & Alford, 2014; Crystal et al., 2013). Treatment with paclitaxel did not impair episodic memory in a source memory task, even after a long retention interval, or the development of proactive interference (Smith, Slivicki, Hohmann, & Crystal, 2017). However, paclitaxel-treated rats showed deficits in their sensitivity to changes in experimental contingencies, as assessed by reversing the source memory rule (Smith et al., 2017), a finding consistent with chemotherapy-induced reductions in cognitive flexibility.

Learning is another domain of cognition that is affected in chemotherapy patients. Notably, rule learning is a feature embedded in the source memory task used by Smith and colleagues (Smith et al., 2017). Because the source information rule reversal represented both new learning and reversal learning, it is still an open question as to whether chemotherapy impaired new learning, reversal learning, or both. An experimental design that dissociates new learning and reversal learning is therefore required to better understand cognitive deficits associated with paclitaxel-induced CICI.

Episodic memory can also be studied in rats by exploiting their well-established proficiency with odors (Panoz-Brown et al., 2016). In the item-in-context olfactory memory approach (Panoz-Brown et al., 2016), rats have been shown to remember multiple unique events and the contexts in which events occurred using episodic memory, all assessed under conditions that dissociated item in context memory from familiarity cues (Panoz-Brown et al., 2016). The olfactory preparation is also well suited for assessing multiple dimensions of cognition, including prior learning, new learning, and reversal learning (Galizio, 2016; Galizio, Miller, Ferguson, McKinney, & Pitts, 2006). However, it is not known if chemotherapy treatment differentially affects new learning and/or reversal learning. The current work presents the opportunity to validate and expand on whether paclitaxel treatments spare episodic memory and impairs learning (Smith et al., 2017).

Severity of unwanted side effects is often a dose-limiting factor for clinical use of paclitaxel (Scripture, Figg, & Sparreboom, 2006). Meanwhile, not all studies of CICI have found impairments after chemotherapy treatment (Fremouw, Fessler, Ferguson, & Burguete, 2012a; Fremouw, Fessler, Ferguson, & Burguete, 2012b; Long et al., 2011; Lyons, Elbeltagy, Bennett, & Wigmore, 2011). These inconsistencies across chemotherapy drugs highlight the importance of examining multiple domains of learning and memory. Multidimensional approaches serve to better characterize the pattern of spared and impaired aspects of treatment induced cognitive impairment and their underlying mechanisms.