5-Fluorouracil counters melatonin-induced alterations in locomotor activity

L. Cassim and S. Daya
Neuroscience Research Group, Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa, S.Daya@ru.ac.za

Introduction

5-Fluorouracil (5-FU) is a commonly-used antineoplastic agent associated with a wide range of toxicities, particularly to the gastrointestinal, immune and haematological systems [1]. Clinical studies have shown that the co-administration of the antioxidant and pineal hormone melatonin to cancer patients on 5-FU therapy both significantly enhances the quality of life of these patients and attenuates 5-FU-induced toxicity, leading to an increase in patient survival time [2]. Having previously reported that melatonin counters 5-FU-induced decreases in brain neurotransmitter levels [3], and given the paucity of information available on the effects of 5-FU on locomotor activity, we decided to investigate the effects of these drugs on a variety of locomotor activity parameters. Alterations in locomotor activity are very common in cancer patients [4, 5], who are known to have lowered endogenous levels of melatonin [6]. Such an investigation would offer insight into whether 5-FU potentially exacerbates these locomotor activity changes, contributing to the development of "chemotherapy-related malaise" [7], for example, and whether co-therapy with melatonin might counter this.

Method

Thirty-two male Wistar rats, each weighing between 200g and 300g, were divided into four treatment groups of eight rats per group: (i) control, receiving 0.9% saline; (ii) 5-FU, at a dose of 1 mg/ kg; (iii) melatonin, at a dose of 1 mg/ kg; and (iv) a group receiving both drugs, each at a dose of 1 mg/ kg. The animals were injected three times a day for five days. Locomotor activity was measured prior to drug treatment, for a twelve hour period of constant bright light, from 07h00 to 19h00, using the Noldus Ethovision® video-tracking system. The parameters investigated were: (i) total distance moved; (ii) maximum distance moved; (iii) mean velocity; (iv) total duration of movement; and (v) rearing frequency. Locomotor activity was similarly measured subsequent to the five days of drug treatment. One-way analysis of variance, followed by the Student-Newman-Keuls multiple range test, was used to determine if there were any statistically significant differences in the pre- and post-treatment locomotor activities of rats across the groups.

Results and discussion

Melatonin administration decreases rearing frequency and the total duration of movement, possibly due to the benzodiazepine-like sedative effects of the compound [8, 9]. The ability of melatonin to decrease the frequency of rearing, an indicator of aggressive behaviour [10, 11] suggests that melatonin has anti-aggressive effects. The administration of 5-FU alone significantly increases the locomotor activity of rats exposed to twelve hours of constant bright light, evidenced by increases in the total distance moved, total duration of movement and mean velocity. This excitatory effect suggests that 5-FU may induce anxiety and/ or depression in the clinical setting. This could be a behavioural effect of the alteration in neurotransmitter levels that we have reported before, in particular due to a fall in serotonin, dopamine and norepinephrine levels [3]. The co-administration of 5-FU to rats receiving melatonin treatment abolishes the effects of melatonin on locomotor activity. This implies that whilst melatonin co-therapy is potentially useful in cancer patients, to normalise physiological parameters and enhance patients' quality of life by strengthening impaired circadian rhythms, inducing sleep, and exerting anti-depressant, anti-aggressive and anxiolytic effects, it is necessary to administer this agent on a chronic basis in order to effectively counteract the adverse effects of 5-FU.

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