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Effect of Xanthone Derivatives on Animal Models of Depression

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ABSTRACT

Background: Extracts of the plant *Hypericum perforatum* L. have been traditionally used in folk medicine for the treatment of depressive disorders. Xanthone, a component of *Hypericum perforatum* L., has been shown to be effective in animal models of depression.
Objective: We investigated if 2 xanthone derivatives (1101 and 1105) were as effective as venlafaxine, which is a serotonin–norepinephrine reuptake inhibitor and was used as a positive control, in animal models of depression.
Methods: A series of derivatives from xanthone were designed and synthesized. After preliminary experiments, 2 xanthone derivatives (1101 and 1105) were considered to be effective in our mouse depression model. To further determine their effects on depression, classical behavioral despair animal models (forced swim and tail suspension tests) were used to assess the efficacies of these derivatives, whereas venlafaxine hydrochloride was used as a positive control. Oral acute toxicity studies were used to determine if the derivatives were toxic in mice.
Results: The oral acute toxicity studies of 2 xanthone derivatives (1101 and 1105) did not show any toxic effect until the dose at 1000 mg/kg body weight, and xanthone derivatives 1101 and 1105 resulted in a significant decrease of the immobility period (in seconds) compared with the untreated control group during the forced swim test with rats (dose = 12 mg/kg; $P < 0.05$) and mice (dose = 25 mg/kg; $P < 0.001$). At lower doses, derivatives 1101 and 1105 also decreased the immobility period of rats and mice during the forced swim test but significant differences were only found in mice compared with the untreated control group ($P < 0.05$). No difference was found between the groups treated with xanthone derivatives and the positive control group during the swimming period in both mice (dose = 25 mg/kg) and rats (dose = 12 mg/kg) ($P > 0.05$). In the tail suspension test, derivatives 1101 and 1105 produced marked effects with regard to the motion of mice ($P < 0.01$ or 0.001, respectively) and the derivatives were also noted to have some effects on rats at a dose of 12 mg/kg ($P < 0.05$). Compared with the positive venlafaxine control group, no differences were found between those treated with either derivative 1101 or derivative 1105 and venlafaxine ($P > 0.05$).
Conclusions: Within certain dose ranges, xanthone derivatives 1101 and 1105 have similar effects to venlafaxine hydrochloride in the treatment of depression as suggested by behavioral despair animal models using rats and mice.

Introduction

Depression is a common mental disorder characterized by pronounced and long-lasting depressed mood, as well as a variety of additional symptoms (behavioral, affective, and cognitive). The number of patients with depression has increased dramatically in recent decades and, according to the World Health Organization, it is projected to become the second largest contributor to the global burden of disease by the year 2020.[1]

Drug treatment is 1 of the most effective tools used to deal with depression. At present, a variety of antidepressant medications are available that have shown beneficial effects. However, all are known to exert adverse side effects, and some are very expensive. Additional treatment modalities with little risk, credible benefit, and moderate costs would be useful additions to depression management.

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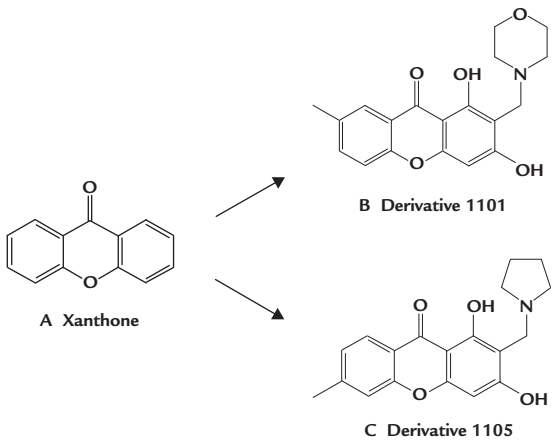

Fig. 1. Chemical structures of (A) xanthone, and the derivatives of (B) xanthone 1101 and (C) xanthone 1105 used in this study

Chinese herbal medicine has been considered a source from which such compounds could be selected for investigation.[2] In recent years, *Hypericum perforatum* L. (HPL) has become a focus of research interest and investigated for its therapeutic effects with regard to mood disorders, and its antidepressive action has been demonstrated in animals and humans.[3] Consequently, in Germany, extracts of HPL have been licensed for the treatment of depression. Indeed, HPL extracts have been found to be more effective than placebos in the treatment of mild to moderate depression,[4] and as effective as several tricyclic antidepressants and fluoxetine.[5] The antidepressant activity of HPL is thought to stem from the presence of flavonoids. Xanthone (**Figure 1A**) is 1 such flavonoid, and can be isolated from the aerial parts of HPL.[6] Furthermore, xanthone has been shown to be a prototype drug useful in the treatment of depression,[7] and its derivatives have been shown to have potential antidepressant activity via forced swim tests (FSTs).[8]

To modify the structure of xanthone and promote its activity to compete with selective serotonin reuptake inhibitors in terms of efficacy, a series of xanthone derivatives were designed and synthesized in this study. After preliminary experiments, 2 derivatives (1101 and 1105) (**Figure 1B–1C**) were considered to be effective following mice swimming test models. Subsequently, FSTs and tail suspension tests (TSTs) were used to detect their effects with regard to depression in rats and mice. Our results suggest that the 2 derivatives effectively improve behavioral despair symptoms in rats and mice compared with negative controls and may be as effective as venlafaxine at certain doses.

Materials and Methods

Animals

Male imprinting control region mice weighing between 18 and 22 g were commercially obtained from the Sino-British SIPPR/BK Lab (Shanghai, China). Male Wistar rats weighing between 150 and 170 g were obtained from the experimental animal center of the Military Medical Science Academy of the Chinese People's Liberation Army (Beijing, China). The animals were maintained under a standard 12-hour light/dark cycle (lights on at 8:00 AM) at a constant temperature of 22°C (±1°C) and mean (SD) relative humidity of 45% (15%) with free access to food and water, except for periods of water and food deprivation. Animals were acclimatized to laboratory conditions before the experiment. Each animal was used only once. The experiments were performed between 9:00 AM and 3:00 PM. The procedures in this study were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Maximal effort was made to minimize animal trauma and the number of animals necessary for the acquisition of reliable data. All experiments were approved by our local ethics committee.

Oral acute toxicity studies in mice

The derivative (1101 or 1105) was weighed and resuspended with 0.5% hydroxymethyl cellulose aqueous solution to obtain the desired concentrations. Mice were starved overnight (16 hours) before feeding with a single oral dose of derivative. Animals were divided into 7 groups of 10 (5 males and 5 females for each group). Mice in each group were fed derivatives (1101 or 1105) at a single oral dose of 250, 500, or 1000 mg/kg body weight for each derivative, respectively; the control group received a single oral dose of 0.5% hydroxymethyl cellulose aqueous solution. General behavior of each mouse was observed continuously for 1 hour after each dose, intermittently every 4 hours for three times, and thereafter over a period of 24 hours.[9] Animals were observed for up to 14 days for any sign of toxicity (eg, behavior change related to central nervous, cardiovascular, and gastrointestinal systems), body weight change, and water and food consumption. At the end of the observation period, all animals were sacrificed under ether anesthesia and vital organs (heart, lung, liver, spleen, and kidney) were removed from all animals for gross and histopathologic examination.

FST

Mice were individually forced to swim inside a polycarbonate cylinder (height = 24 cm; diameter = 16 cm) containing 20 cm water at 25°C. Mice were allowed to swim for a total of 6 minutes; a camcorder (Sony Handycam; Sony Corporation of America, New York, New York) recorded the swim session. Digital video output was analyzed by a computer running SMART Video Tracking System software (Panlab, Barcelona, Spain). The swimming time during the experiment was measured with SMART software. It should be noted that the water was changed before the next animal was placed into the cylinder. Clean water was used for each behavior trial because used water has been shown to alter behavior due to an alarm signal.[10] Mice were returned to cages after testing and dried.

The modified rat FST described by Lucki[11] suggests that rats should swim for 15 minutes in a polycarbonate cylinder (height = 46 cm; diameter = 21 cm) containing 30 cm water at 25°C, with a 5-minute test period recorded. In our study we modified this protocol and allowed rats to swim for 12 minutes. The swimming sessions were recorded by camera but only the final 8 minutes were analyzed by a SMART Video Tracking system. In accordance with the mouse FST protocol, the water was changed after each animal was tested, and rats were returned to the cages after swimming and dried.

TST

The TST was carried out according to the method of Steru et al.[12] Mice were suspended on a small metal hook fixed on the top of a box via adhesive tape placed approximately 1 cm from the tip of the tail. The duration of the immobility period was recorded with a SMART system. The recordings were performed for a total of 6 minutes and data were analyzed with SMART software.

The TSTs with rats were performed as described above for mice; however, the recording time was 9 minutes. The final 6 minutes of the process were analyzed with SMART software.