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Effects of chronic bryostatin-1 on treatment-resistant depression in rats

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ABSTRACT

Despite over a half-century's intensive research worldwide, the currently available antidepressants remain sub-optimal. Therapeutic options for treatment-resistant depression, for instance, are rather limited. Here, we found that rats exhibited a lasting treatment-resistant depressive immobility in response to open space swim test at a high intensity of induction. The induced depressive behavior is associated with a dramatic impairment in spatial learning and memory. Both the depressive immobility and impairment in spatial learning and memory are sensitive to a period of chronic treatment with bryopstatin-1, a relatively selective activator of protein kinase Cε. Bryostatin-1-like analogues therefore might have therapeutic values for the treatment of treatment-resistant depression.

1. Introduction

Major depressive disorder is one of the most prevalent forms of mental illness in humans, with prevalence rate of 16.2% in the United States (Kessler and Bromet, 2013). The disorder is associated with high morbidity and risk of premature mortality (Nestler et al., 2002; Ursano et al., 2015) and is predicted to be the leading cause of disability in Western countries by 2030 (Mathers and Loncar, 2006). Despite intensive research worldwide since antidepressant drugs were introduced into clinical practice over a half-century ago, there has been almost no progress in developing new drugs through novel targets (Mathew et al., 2008; Belzung, 2014). At least 30% of patients with major depressive disorder do not show effective therapeutic benefits to the available antidepressants (Ionescu et al., 2015). The non-responsive cases were termed as treatment-resistant depression, or refractory depression (Fava, 2003), and remain a tough clinical challenge today. Recently, blocking glutamatergic system in the hippocampus (Lefebvre et al., 2017), such as by using a low dose of ketamine, a potent non-competitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist, has been shown to produce rapid-onset antidepressant efficacy (Wang et al., 2015; Bobo et al., 2016). The glutamatergic system in the brain is widely involved in cognition and regulation of behaviors. The potential problems with these antagonists as antidepressants include the facts that their intended selectivity for targeting negative memory is only partial at most and that the efficacy of ketamine tends to wear off in time, in addition to other adverse effects (Wan et al., 2015). Long-term impacts on memory operation and retrieval also need to be carefully evaluated, especially when a continuation-phase administration of i.v. ketamine infusions is necessary (Vande Voort et al., 2016). On the other hand, there is substantial evidence supporting acute efficacy of electroconvulsive therapy in treatment-resistant depression. Unfortunately, memory loss and the need for repetitive treatments preclude its use as a long-term treatment option.

We have observed that when facing an open space, no-escape water environment, depressive immobility would quickly dominate in rodents' behavior after an initial (failed) intensive search for an escape (Sun and Alkon, 2013). The impacts of the open space swim test on behavior are age-, sex-, and intensity (duration)-dependent (Sun and Alkon, 2008). In the present study, we directly evaluate whether induction at high intensity (longer duration) would lead to depressive behavior mimicking treatment-resistant depression and whether chronic bryostatin-1 treatment, if induced, might be effective against the treatment-resistant depressive immobility in animals. It has been well established that protein kinase C is involved in the regulation and control of many types of memories (Alkon et al., 2005). Bryostatin-1, a relatively specific protein kinase C (PKC)ε activator, enhances the expression and activity of brain-derived neurotrophic factor in the hippocampus (Sun et al., 2015) and reverses the induced treatment-resistant depressive immobility. Furthermore, our results show that the induced depressive behavior mimics the human disease, exhibiting a

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dramatic impact on the ability of learning and memory. Based on the results presented above, chronic bryostatin-1 might have therapeutic value for the treatment of treatment-resistant depression.

2. Materials and methods

2.1. Animals and drug treatment

Adult male Wistar rats (175–200 g) were housed two per cage in a temperature-controlled (20–24 °C) room for at least a week prior to experimentation, allowed free access to food and water, and kept on a 12-h light/dark cycle.

Chronic effects of imipramine and bryostatin-1 on induced immobility were evaluated, starting 24 h after the last trial of the 3 open space swim test trials. Imipramine (Sigma), a prototypical tricyclic antidepressant, was chronically used as a standard antidepressant (15 mg/kg, i.p., daily for 5.5 weeks). Bryostatin-1 (Sigma) was administered at 20 μg/m^2 (tail i.v., 2 doses/week for 5.5 weeks). The dose of bryostatin-1 was based on our preliminary dose-response studies that smaller doses were ineffective against disorders-induced synaptic and cognitive impairments. Non-treated groups received the same volume of vehicle at the same frequency.

All procedures were conducted according to National Institutes of Health Animal Care and Use Committee guidelines, and were approved by the Ethical Committee of the Institute.

2.2. Open space swim test: induction of depressive behavior

Rats were placed individually in a round pool, which has a diameter of 152 cm and height of 60 cm and was filled with 40 cm H_2O (24 ± 1 °C). No escape was provided in these trials during the test. Rats were free to swim (or not to swim) for 24 min and then removed and returned to their home cages after drying. The observer(s) were obscured from sight of the rats during the trials, but were able to observe the animals' behaviors on a PC monitor during the trials. The same procedure (24 min session/day) was followed 24 h later for 2 more days. The induction of depressive immobility is age- and sex-dependent (Sun and Alkon, 2008). The session of 24 min represents 2 fold of the duration (thus intensity; Sun and Alkon, 2008) needed to induce a significant depressive immobility in the male rats at the age when they were tested. The swimming/drifting path was recorded with a video-tracking system (Poly-Track Video Tracking System, San Diego Instruments, Inc.). The distance moved (mobility) includes all the distance moved during the entire 24 min, as caused by active swimming/searching as well as slow drifts. We have previously reported that the swim activity monitored accurately reflects duration of mobility and that the maximum effect is induced on the third trial (Sun and Alkon, 2003). For evaluating a long-term impact, the induction was followed by 'monitoring' sessions (24 min) at a frequency of 1/week (Sun and Alkon, 2004).

2.3. Spatial water maze learning and memory task

Effects of the induced depressive behavior on spatial learning and memory were evaluated with the Morris water maze task, in a 152 cm-diameter pool (24 ± 1 °C). The maze was divided into four quadrants. Control rats were allowed to swim for 2 min in the pool without a hidden platform, the same day when the other groups were on their last monitoring session. Twenty-four h later, all rats were trained for 2 trials/day for 4 days to find a hidden platform (9 cm diameter). The platform was centered in one of the quadrants and submerged about 2 cm below the water surface. At the start of all trials, rats were placed in the water facing the maze wall, using different starting positions, and allowed to swim until they found the platform, where they remained for 20 s. Any rat that failed to find the platform within 2 min was guided there, with the maximum latency of 120 s scored. The swimming path was recorded by a video-tracking system, which computed latency to find the platform, distance swum, heading angle, and percentage of time spent in the quadrants.

After the training trials, a probe trial of 60 s was given 24 h after the last trial, with the platform removed, to assess memory for platform location by the distance swum in the quadrants.

2.4. Visible platform test

After the probe trial of the water maze task, rats were tested on a visible platform task (a non-spatial task; with the platform marked with a pole that protruded 9 in. above the water surface but at a new location) to evaluate their sensorimotor ability and motivation for an escape. The latency to reach the visible platform was recorded and compared between different groups.

2.5. Statistic analysis

Statistical analysis was performed using the analysis of variance (a two-way ANOVA), followed by Newman-Keuls multiple comparisons test, wherever appropriate. $P < 0.05$ was considered significant.

3. Results

3.1. Open space swim test induces depressive immobility in rats

The open space swim test (24 min/one trial/day for 3 days) induced a significant immobility, which lasted for at least 1 week without further sessions and weeks with separate open space swim test monitoring episodes (1/week) after the initial 3 induction sessions (Fig. 1). Typically, rats would initiate active swim in the first min and gradually developed into intermittent periods of immobility, which lasted longer and longer as the session continued. Without an effective treatment, a rat in the immobility phase did not make any movements other than those just sufficient to keep its head above the water surface (Fig. 1 inset), a characteristic behavior of depression similar to those reported in the forced swimming test, as we described previously (Sun and Alkon, 2004). Imipramine, as the standard antidepressant to determine the sensitivity to antidepressant treatment, and bryostatin-1 were administered chronically to evaluate their impacts on the induced immobility. The results after the initial 3 induction sessions showed a significant group difference with the treatments (group data points 4–8; $F_{2,191}$=10.12, $P < 0.001$), whereas the initial OSST sessions induced similar effects on the distance traveled among the groups (in the first three sessions: $F_{2,71}$=0.668, $P > 0.05$). The chronic treatment with imipramine did not reduce the immobility as compared with the vehicle group ($F_{1,127}$=0.892, $P > 0.05$), indicating a depressive behavior with the treatment-resistant profile. Bryostatin-1, on the other hand, was effective in reducing the mobility ($F_{1,127}$=12.033, $P < 0.001$; compared with the vehicle group), although 2–3 weeks of treatment were needed to produce the therapeutic effects, which lasted 2.5 weeks after the last dose (the longest duration measured; Fig. 1).

3.2. Effects of induced depressive behavior on spatial learning

One day after the last monitoring session (Fig. 1), we tested the ability of three groups of rats: vehicle-induction, induction-Bry, and control (age-matched but without the induction), in spatial learning and memory, using the hidden-platform water maze. As shown in Fig. 2A, the speed and the extent of the learning were significantly different among the groups ($F_{2,191}$=15.431, $P < 0.001$), indicating that spatial learning in the rats after depressive behavior induction was significantly impaired, severer than the impairment associated with shorter session-induced depressive immobility (Sun and Alkon, 2004). Chronic bryostatin-1, however, essentially rescued rats' ability in spatial learning ($F_{1,127}$=0.912, $P > 0.05$; compared with the control without the behavioral induction).

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