Effects of Wallpaper with the Ability of Photo-Activated Releasing Fragrance on Central Nervous System

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Fragrances can relax us and bring a good spirit for us. But they cannot produce these results or produce the opposite results if the concentrations of fragrances in the air are large due to their strong volatility. To overcome this obstacle, mesoporous silica nanospheres with the ability of photo-activated releasing sandela 803 (MS-S@S803) were prepared. And the effects and internal mechanism of MS-S-W@S803 on CNS were study from behavioural level, tissue level, cell level and molecule level. MS-S-W@S803 could relieve the stress and beat the anxiety. Besides, it could also stimulate the neural activity of hippocampus, hypothalamus and olfactory bulb regions at a higher intensity. In addition, the abilities of nerve regenerations in corpus striatum, substantia nigra and olfactory bulb were increased by MS-S-W@S803. And the expressions of DOPA, Ach, GABA and NMDA were also facilitated by MS-S-W@S803. Interestingly, the anxiolytic effects were more significant as time progresses.

KEYWORDS: Fragrance, Photo-Activated Release, Central Nervous System, Neural Activity, Nerve Regeneration.
from nanocarriers mainly depends on the de-interactions between fragrances and nanocarriers. But most of the processes of these interactions and de-interactions are irreversible. In other words, with the interactions gradually decreased, the release of fragrances are gradually rapider. So the processes of interaction and de-interaction are best to reversible. However, it is far from enough to slowly release the fragrance. If the fragrances are released at any time, the fragrances loaded nanomaterials will not be able to be stored. And sometimes we need not smell these aromas, such as when we sleep in the dark. Besides, these nanomaterials can also be stored in the dark. Therefore, it is necessary and urgent to develop reversible and sensitive light-induced nanomaterials for the fragrances.

In this study, photo-activated mesoporous silica nanospheres loaded with sandela 803 (a kind of representative synthetic santalum album essential oil) were designed, prepared and named as MS-S@S803. As shown in Figure 1, the pure mesoporous silica nanospheres were prepared via sol–gel method. The azobenzene derivatives were then modified on the mesoporous wall of silica nanoparticles to obtain MS-S. Besides, sandela 803 was added into the mesoporous via physical absorption. In the dark, the azobenzene derivatives on the mesoporous wall were regarded as fences to prevent the sandela 803 from releasing.20 In the light, photoinduced cis-trans isomerizations of N=N bonds caused the dynamic motion of azobenzene derivatives.21 And the azobenzene derivatives were thus served as brooms to sweep the guest molecules out. In the following, the MS-S@S803 was applied to wallpaper and named as MS-S-W@S803. The MS-S-W@S803 was then glued on the wall of mouse cage to mimic the wall of our house.

The effects of pure sandela 803 treated wallpaper and MS-S-W@S803 on CNS of mice were explored from four levels. Firstly, the elevated plus maze and open field test were performed to determine whether there were effects on CNS in behaviour level, which was the premise of the detection in other three levels. In tissular level, the neural activities were analysed via the measurement of neuopotentials in certain brain areas. In the following, the nerve regenerations of certain brain areas was detected via Brdu staining in cellular level. Finally, the expression of some neurotransmitters was measured in molecular.

**EXPERIMENTAL REAGENTS AND INSTRUMENTS**

Sandela 803 was obtained from Shanghai research institute of fragrance and flavor industry. (3-Isocyanatopropyl)
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Table I. The conditions of LC.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow velocities (mL/min)</th>
<th>Methanol (0.1% FA) (%)</th>
<th>Water (0.1% FA) (%)</th>
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<tr>
<td>0.8</td>
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</tr>
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<td>2</td>
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<tr>
<td>3</td>
<td>0.35</td>
<td>2</td>
<td>98</td>
</tr>
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</table>

Triethoxysilane (ICPES), acetylcholine (Ach) chloride, γ-aminobutyric acid (GABA) and dopamine (DOPA) hydrochloride were obtained from Alfa Aesar. 4-aminoazobenzene was obtained from Tokyo Chemical Industry (TCI). Superdry tetrahydrofuran (THF) was purchased from J&K Scientific Ltd. Hexadecyltrimethylammonium bromide (CTAB), Tetraethyl orthosilicate (TEOS), ammonium hydroxide (28% solution in water), N-methyl-D-aspartic acid (NMDA), formic acid (FA) and extra dry toluene (PhMe) were obtained from Acros Organics.

Preparation of Photo-Driven Wallpaer Loaded with Sandela 803 Based on Mesoporous Silica Nanospheres (MS-S-W@S803)

AZO (1380.68 mg) and ICPES (1731.52 mg) were dissolved into anhydrous and then refluxed at 80 °C for 24 h. The crude product was purified by recrystallization in hexane at −20 °C to obtain ICPES-AZO. Mesoporous silica was prepared via a sol–gel method. In brief, CTAB (1000 mg) and 28% ammonium hydroxide (25 mL) were dispersed into deionized water (336 mL) and heated to 80 °C for 30 min. TEOS (6.55 mL) was then added into the solution for 2 h at 80 °C. The precipitate was collected, calcined at 550 °C for 5 hours and dispersed into anhydrous PhMe (125 mL) with ICPES-AZO (125 mL) and refluxed at 80 °C for 24 h. The particles (MS-S@S803) was collected and dispersed into deionized water. Sandela 803 was added into the aqueous solution under stirring for 24 h in the light. And the solution was then dialyzing in a Cellu SepH1-membrane (MWCO 7000) against deionized water in the dark to obtain MS-S@S803. Finally, wallpaper were immersed in MS-S@S803 aqueous solutions (1 mg/mL) under stirring. After 12 h, the wallpaper was then dried at 40 °C for 1 h in an oven to obtain MS-S-W@S803.

Animals

Female C57 mice (3 weeks and 6 weeks, respectively) were purchased from the Academy of Military Medical Sciences of China. The MS-S@S803 treated wallpaper (MS-S-W@S803), pure sandela 803 treated wallpaper (W@S803) and untreated wallpaper (pure W) were glued on the three side wall of mouse cage. The younger mice were cultured for 7 days and the older mice were cultured for 30 days.

![Figure 2](image-url)  
(A) The reaction formula of ICPES-AZO. (B) The 1H NMR spectra of ICPES-AZO.
Behaviouristics Tests
Open field test and elevated plus maze were performed to test the effects on behaviouristics of mice. The open field was a box (48 cm × 48 cm). Mice were put into the center of open field and the movement information was recorded. The elevated plus maze composed of two open arms and two closed arms (10 cm × 50 cm) with an open roof arranged such that the two arms of each type were opposite to each other. The maze was 50 cm high. Mice was put into the center of elevated plus maze and the movement information was recorded.

Electrophysiology Test
Mice were anesthetized by isoflurane and their head was then placed on a stereotaxic apparatus under isoflurane by isoflurane and the skull were exposed. The hippocampus, hypothalamus and olfactory bulb regions were located via The Mouse Brain: In Stereotaxic Coordinates. The electrodes were insert into the above-mentioned brain regions and the electrophysiology signals were recorded via a physiological recorder (Techman Soft, China).

Immunohistology
Brains were rapidly excised and fixed in 4% (w/v) paraformaldehyde after the mice were sacrificed. The fixed samples were then embedded in paraffin blocks to prepare tissues sections at a thickness of 5 μm. After deparaffinization, the brain sections were stained with anti-BrdU antibody and DAPI. The images were visualized by an optical microscope. The magnification used in the experiment was 20×.

Expression of Neurotransmitters
The contents of neurotransmitters was measured via liquid chromatography-mass spectrometry (LC-MS). Firstly, brain tissues were weighed and physiological saline was added and homogenized to obtain a brain homogenate sample (0.2 g/mL). 50 μL of brain homogenate sample was then added into 305 μL of methanol, fully whirled for 3 min and centrifuged at 4000 r/min for 10 min. Finally, 100 μL of supernatant was taken to test by LC-MS. The chromatographic column was Polar RP column (3 mm × 50 mm ID., 2.6 μm, Phenomenex) at 40 °C. The mobile phase A was methanol containing 0.1% FA. The mobile phase B was deionized water containing 0.1% FA. The mobile phase condition was shown in Table I. The peaks

Figure 3. The fourier transform infrared spectroscopy. (a) ICPES-AZO; (b) pure mesoporous silica nanocolumns; (c) MS-S.

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Figure 4. The TGA results. (a) ICPES-AZO; (b) MS-S; (c) pure mesoporous silica nanospheres, (e) the content of ICPES-AZO in MS-S.

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Figure 5. The TEM images of (A) MS-S and (B) MS-S@S803.

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Figure 6. The cumulative release profiles of sandela 803 in different samples. (a) Wallpaper treated with free sandela 803 in the dark; (b) MS-S-W@S803 in the light; (c) MS-S-W@S803 in the dark. The mean ± SD is shown (n = 3).

Figure 6. The cumulative release profiles of sandela 803 in different samples. (a) Wallpaper treated with free sandela 803 in the dark; (b) MS-S-W@S803 in the light; (c) MS-S-W@S803 in the dark. The mean ± SD is shown (n = 3).
of DOPA, Ach, GABA and NMDA was at 0.56, 0.56, 0.53 and 0.57 minutes, respectively.

**Statistical Analysis**

All data were expressed as mean ± SD unless otherwise indicated. Statistical significance was analyzed using one-way ANOVA. Statistical differences in behavioral data were determined using two-way repeated measure ANOVA.

**RESULTS**

**Characterisation of MS-S@S803**

Before azobenzene molecule were modified into mesoporous silica nanospheres, they needed to be linked to the silane coupling agent ICPES. The synthetic route was shown in Figure 2(A). ICPES-AZO was synthesized by a condensation reaction of ICPES with AZO. The product was identified by 1H NMR spectra. As shown in Figure 2(B), the photo-responsive molecule ICPES-AZO was prepared successfully. 1H NMR (600 MHz, CDCl3, δ): 0.68 (t, 2H, Si–CH2–), 1.23 (t, 9H, –CH3–, –CH3–), 1.70 (m, 2H, –CH2–), 3.30 (t, 2H, –CH2–NH–), 3.72 (m, 2H, –NH–CO–NH–), 3.83 (m, 6H, –Si–O–CH2–), 7.44 (t, 1H, aryl H), 7.50 (t, 4H, aryl H), 7.89 (d, 4H, aryl H).

Pure mesoporous silica nanospheres were modified with ICPES-AZO to prepare light-activated mesoporous silica nanospheres (MS-S). The chemical structures of pure mesoporous silica nanospheres, ICPES-AZO, and MS-S...
were detected by fourier transform infrared spectroscopy (Fig. 3). There was no obvious characteristic peak in pure mesoporous silica nanospheres, which indicated that the CTAB template can be completely removed. Besides, MS-S displayed a park of peaks of ICPES-AZO. The peaks at 2930 and 2826 cm\(^{-1}\) were attributed to –CH\(_2\). The peak 1560 cm\(^{-1}\) was attributed to the stretching vibration of benzene ring. But there were no peaks at 2975 and 2892 cm\(^{-1}\), which indicated that there was no free ICPES-AZO due to the absence of –CH\(_3\). These results demonstrated that all the ICPES-AZO was modified into the MS-S.

The content of photosensitizer was then measured via thermogravimetric analysis (TGA). As shown in Figure 4, ICPES-AZO was almost completely decomposed between 200 and 320 °C. The pure mesoporous silica nanospheres were not decomposed between 50 and 500 °C. The MS-S had the same decomposition period as ICPES-AZO. This results indicated that ICPES was successfully linked to mesoporous silica nanospheres and the content of ICPES-AZO in MS-S was 35.21% according to the TGA data.

The surface morphology of MS-S was detected by transmission electron microscope (TEM). As shown in Figure 5(A), MS-S was spherical with diameter of about 80 nm. Both of the morphology and size were homogeneous and there were pores in the MS-S. After loading sandela 803, as shown in Figure 5(B), the size and morphology remain unchanged and homogeneous. And there were also pores in MS-S@S803 probably due to the low contrast of sandela 803.

![Figure 8](image)

Figure 8. Representative tracks of movement patterns of different samples in elevated plus maze. The green curves represented the movement of mice. (B–H) The quantitative results of Figure 3(A). The mean ± SD is shown (n = 3). *P < 0.05, **P < 0.01, ***P < 0.005.
As shown in Figure 6, free sandela 803 was rapidly released from the wallpaper. And the release amount of sandela 803 reached 20.64% after 8 days. When the wallpaper treated with MS-S@S803, the release rate of sandela 803 was significantly reduced both in the dark and in the light, which indicated that MS-S@S803 had an excellent slow-release effect. When the MS-S-W@S803 was in the light, 7.65% of sandela 803 was released from the wallpaper after 8 days. By contrast, only 1.36% of sandela 803 was released in the dark, which indicated that MS-S-W@S803 had a distinguished photo-responsive release property. Above all, MS-S-W@S803 had excellent sustained and controlled release performances.

Effects on Behaviouristics
Open field and elevated plus maze were performed to analyse the effects on behaviouristics of mice. As shown in Figure 7(A), the movement distances of pure sandela 803 treated wallpaper (W@S803) group were little longer than the movement distances of untreated wallpaper (pure W) group after 7 days and 30 days. Besides, the movement distances of MS-S@S803 treated wallpaper (MS-S-W@S803) were much longer than others. And compared with cultured for 7 days, the movement distance were longer for 30 days. In the following, the movements distance in the center of open field (zone 5) and its ratio were quantified. As shown in Figures 7(B)–(H), after 7 days, the movement distance in zone 5 and its rate of MS-S@S803 group were 1106.87 mm and 3.97%, respectively. While after 30 days, the movement distance in zone 5 and its rate were increased to 1544.09 mm and 7.10%, respectively. For W@S803, they were only 1133.62 mm and 4.95%, respectively.

Figure 9. The electrophysiology signals cultured with different samples for 7 days in (A) hippocampus, (C) hypothalamus, (E) olfactory bulb and the quantitative results in (B) hippocampus, (D) hypothalamus, (F) olfactory bulb. The mean ± SD is shown (n = 3). *P < 0.05, **P < 0.01, ***P < 0.005.
The results of elevated plus maze were shown in Figure 8(A). There were distinct differences in the movement area and movement distance. As shown in Figures 8(B)–(H), compared with W@S803, MS-S-W@S803 motivated mice to walk on open arms. And compared with 7 days, the positive effects were more significant after 30 days. The movement distances on open arms were increased from 1757.92 mm to 2029.52 mm. And the ratios were increased from 79.83% to 21.60%.

**The Effects on Electrophysiology**

In tissue level, we detected the electrophysiology of hippocampus, hypothalamus and olfactory bulb regions. As shown in Figure 9, after the mice cultured with MS-S-W@S803 for 7 days, the amplitude in all of the hippocampal, hypothalamus and olfactory regions was significantly enhanced. The potential differences in the hippocampal, hypothalamus and olfactory regions were 1953.12, 2035.53 and 1724.24 μV, respectively. After cultured with W@S803 for 7 days, by contrast, the amplitude in all regions was little enhanced. The potential differences were 1483.05, 1492.31 and 1333.62 μV, respectively.

In addition, the amplitudes were measured after the mice cultured for 30 days. As shown in Figure 10, compared with W@S803 group, the amplitudes in all the regions of MS-S-W@S803 group were also increased much more obviously. The potential differences in the hippocampal, hypothalamus and olfactory regions of MS-S-W@S803 group were 3947.53, 2405.27 and 1876.83 μV, respectively, while the amplitudes in W@S803 group were only 2526.04, 1650.06 and 1178.44 μV, respectively.

In the following, the comparisons of quantitative electrophysiology signals cultured for between 7 days and 30 days were shown in Figure 11. Compared with cultured for 7 days, the amplitudes in hippocampus and hypothalamus regions of MS-S-W@S803 group after 30 days were larger than that after 7 days.

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**Figure 10.** The electrophysiology signals cultured with different samples for 30 days in (A) hippocampus, (C) hypothalamus, (E) olfactory bulb and the quantitative results in (B) hippocampus, (D) hypothalamus, (F) olfactory bulb. The mean±SD is shown (n = 3). *P < 0.05, **P < 0.01, ***P < 0.005.
The Effects on Nerve Regeneration

The abilities of nerve regeneration were detected via immunofluorescent staining with anti-BrdU antibody. As shown in Figure 12(A), in corpus striatum, the ability of nerve regeneration was a little increased after cultured with W@S803 for 7 days. After cultured with MS-S-W@S803, by contrast, the ability of nerve regeneration was enhanced significantly. And after 30 days, the effects on nerve regeneration were more remarkably. The effects on substantia nigra were shown in Figure 12(B). There were few proliferative nerve cells after cultured with W@S803 for 7 days. But there were plenty of proliferative nerve cells after cultured with MS-S-W@S803 for 7 days and especially 30 days. For olfactory bulb region, there was hardly any proliferative cells after cultured with W@S803 for 7 days. For MS-S-W@S803, by contrast, the ability of nerve regeneration was increased obviously for 7 days and 30 days. In particular, the effects of MS-S-W@S803 on olfactory bulb were more remarkable than that on other regions.

The Effects on Expressions of Neurotransmitters

The contents of neurotransmitters were measured via LC-MS. As shown in Figure 13, after 7 days, the expressions of all of DOPA, Ach, GABA and NMDA in MS-S-W@S803 group were more than that in W@S803 group. And the contents in MS-S-W@S803 group were 8940, 744, 261000 and 128 ng/g, respectively. After 30 days, by contrast, the contents in MS-S-W@S803 reached 11700, 975, 282300 and 171 ng/g, while the contents in W@S803 were only 9338, 466, 247900 and 98 ng/g, respectively. The results indicated that sandela 803 could enhance the expressions of DOPA, Ach, GABA and NMDA. The photo-responsive MS-S-W@S803 could increase much more expressions of these neurotransmitters than non-photo responsive W@S803. Besides, the effects were more obvious after cultured with MS-S-W@S803 for 30 days.

DISCUSSION

Fragrances can relax us and bring a good spirit for us. But they cannot produce these results or produce the opposite results if the concentrations of fragrances in the air are large due to their strong volatility. To overcome this obstacle, mesoporous silica nanospheres with the ability of photo-activated releasing sandela 803 (MS-S@S803) were prepared. The azobenzene derivative on the wall of mesoporous could cis-trans isomerize in the light, which could impel the guest molecules from the mesoporous as the impellers. And in the dark, the azobenzene derivative could prevent the odorant molecules from escaping as the gatekeepers. The 1H NMR spectra indicated that azobenzene derivatives ICPES-AZO was synthesized successfully. Fourier transform infrared spectra indicated that azobenzene derivatives ICPES-AZO was synthesized successfully. Fourier transform infrared spectra indicated that azobenzene derivatives ICPES-AZO was synthesized successfully.

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Figure 11. The comparison of quantitative electrophysiology signals cultured between 7 days and 30 days. *P < 0.05, **P < 0.01, ***P < 0.005.

Figure 12. The immunofluorescence staining with anti-BrdU antibody in (A) corpus striatum, (B) substantia nigra and (C) olfactory bulb regions. Blue represented cell nuclei and red represented proliferative cells.
the MS-S and the content was 35.21%. The morphology and size were detected via TEM. Both of MS-S and MS-S@S803 were spherical with the diameter of about 80 nm. And the mesoporous were also observed. The MS-S was then added into wallpaper (MS-S-W@S803) and further glued on the wall of mouse cages.

In addition, the effects of MS-S-W@S803 and pure sandela 803 (W@S803) on central nervous system (CNS) were evaluated. Firstly, the effects on behavioristics of mice were detected via open field test and elevated plus maze. When the mice were cultured with W@S803, their movement distances in all regions and especially the center of the open field were slightly increased, which indicated that sandela 803 could relieve the stress of mice.22–23 But the effects were not obvious. When cultured with MS-S-W@S803 for 7 days, the movement distances were remarkably increased. And after cultured for 30 days, the effects were more obvious. These results indicated that MS-S-W@S803 could relieve the stress of mice significantly in the long term. Besides, we also performed elevated plus maze to study the effects. The results showed that compared W@S803, MS-S-W@S803 had a better and long term anxiolytic effect.24–25

In the following, we explored internal mechanism of these effects from tissue level, cell level and molecule level. Firstly, the neural activities in hippocampus, hypothalamus and olfactory bulb were measured via recording the electrophysiology signal in tissue level. Olfaction signal were sent to CNS via olfactory bulb.26–27 For MS-S-W@S803, the potential difference was significantly increased while the potential difference for W@S803 was slighted increased, which indicated that MS-S-W@S803 could strongly stimulate the olfactory nerve. Besides, the amplitude of electrophysiology signal in hippocampus was increased, which indicated that the memory related neural activity was further stimulated.

Figure 13. The expression of neurotransmitters (neurotransmitter/brain, m/m). The expression of (A) DOPA, (B) Ach, (C) GABA and (D) NMDA in the brains of mice cultured with different samples for 7 days. The expression of (E) DOPA, (F) Ach, (G) GABA and (H) NMDA in the brains of mice cultured with different samples for 30 days. The comparison of (I) DOPA, (J) Ach, (K) GABA and (L) NMDA in the brains of mice cultured with MS-S-W@S803 for between 7 days and 30 days. *P < 0.05, **P < 0.01, ***P < 0.005.
by MS-S-W@S803. Additionally, hypothalamus was in charge of internal secretion and mood. And MS-S-W@S803 was also stimulated its activity. So MS-S-W@S803 could relieve the stress and defend against threats and anxiety. Secondly, in the cell level, the nerve regenerations in corpus striatum, substantia nigra and olfactory bulb of mice cultured with MS-S-W@S803 and W@S803 were studied via immunofluorescent staining with anti-Brdu antibody. The abilities of nerve regenerations were a little increased when the mice cultured with W@S803. When cultured with MS-S-W@S803, by contrast, the abilities of nerve regenerations in all of corpus striatum, substantia nigra and olfactory bulb were increased obviously. Corpus striatum took charge of muscular movement and most of dopaminergic neurons were distributed in substantia nigra. These results explained the excellent effects of MS-S-W@S803 on the motor ability and anti-pressure ability in cell level.

Finally, the expressions of neurotransmitters were measured via LC-MS in molecule level. DOPA could create exhilaration and focused attention and NMDA takes part in internal secretion and mood related neural activity. So the increases of DOPA and NMDA in the brain of mice promoted decompressing and good mood when the mice were cultured with MS-S-W@S803 for 7 and 30 days. Ach participates in learning memory and keep our conscious and GABA could participate in the effects of antianxiety.

CONCLUSIONS
In this study, mesoporous silica nanospheres with the ability of photo-activated releasing sandela 803 (MS-S@S803) were prepared and applied to wallpaper (MS-S@W@S803). The effects of MS-S@W@S803 and pure sandela 803 treated wallpaper (W@S803) on CNS were compared. Firstly, the MS-S@W@S803 had more significant effects on the decompression and antianxiety in behavioural level. Secondly, in tissue level, the hippocampus, hypothalamus and olfactory bulb regions were stimulated at a higher intensity when cultured with MS-S@W@S803 for 7 and 30 days. Thirdly, the abilities of nerve regenerations in corpus striatum, substantia nigra and olfactory bulb were increased more remarkably in cell level after cultured with MS-S@W@S803. Fourthly, MS-S@W@S803 promoted the expression of DOPA, Ach, GABA and NMDA. Interestingly, the effects of MS-S@W@S803 on the CNS of mice were long-term.

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