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# Comparison of the Inducing Effect of Indole Compounds on Medusa Formation in Different Classes of Medusozoa

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**Scyphozoa, Cubozoa and Hydrozoa are classes in the phylum Cnidaria that undergo metagenesis involving a dramatic morphological transition. In Scyphozoa and Cubozoa, when exposed to species- or strain-specific transition-inducing stimuli, asexually reproducing benthic polyps transform into sexually reproducing planktonic medusae. In Hydrozoa, exposure to species- or strain-specific transition-inducing stimuli causes formation of medusa buds in the polyp's body. In *Aurelia aurita* (Linnaeus, 1758) (Scyphozoa, Semaeostomeae), polyp-to-jellyfish transition is induced by some simple indole compounds. However, whether indole compounds can induce polyp-to-jellyfish transition in Cubozoa and Hydrozoa remains unknown. In the present study, we show that an indole compound, 5-methoxy-2-methylindole, induces polyp-to-jellyfish transition in Scyphozoa and Cubozoa. This inducing action suggests that the downstream steps of polyp-to-jellyfish transition are regulated by the same biochemical reactions in Scyphozoa and Cubozoa, irrespective of the type of transition-inducing environmental stimuli.**

**Key words:** Cnidaria, Medusozoa, metagenesis, strobilation, indole compounds

## INTRODUCTION

Medusozoa (Staurozoa, Scyphozoa, Cubozoa and Hydrozoa) is a clade of Cnidaria that has one of the most complex lifecycles in the animal kingdom. The phylum Cnidaria is classified into five classes: Staurozoa, Scyphozoa, Cubozoa, Hydrozoa, and Anthozoa. The basic lifecycle of Medusozoa consists of two morphologically different stages: polyp and medusa. In Staurozoa, the upper parts of benthic polyps metamorphose into sexually reproducing medusae (Miranda et al., 2012). In Anthozoa, benthic polyps reproduce both sexually and asexually. In contrast, these two reproduction methods are clearly separated in Scyphozoa, Cubozoa and Hydrozoa. These three classes are characterized by metagenesis, a lifecycle with a transition from an asexually reproducing benthic polyp to a sexually reproducing planktonic medusa. Sexual reproduction is regulated by seasonal and lunar rhythms (Krupp, 1983; McCauley, 1997; Sebens, 1981), whereas asexual reproduction depends on nutritional conditions (Ma and Purcell, 2005). Metagenesis is a type of lifecycle with two generations: an asexually reproducing polyp and a sexually reproducing medusa. The dramatic metamorphosis from polyp to medusa is called "strobilation" in Scyphozoa (Spangenberg, 1967), "metamorphosis" in Cubozoa (Marques and Collins, 2004), and "medusa budding" in Hydrozoa (Uchida and Sugiura, 1977), and is induced by species- or strain- specific environmental stimuli. For example, strobilation of *Aurelia aurita*, one of the most extensively studied Cnidarian species, is induced by a seasonal decrease in water temperature. Under laboratory conditions, polyps of *A. aurita* elongated and several constrictions form in them 3–4 weeks after a decrease of 5°C in the water temperature (Spangenberg, 1967). This stage is called "strobila", and a single strobila metamorphoses into several planktonic ephyra larvae. As another example, Kubota (1996) reported that a decrease in light intensity in the evening triggered medusa budding in *Eugymnanthea japonica* (Yamada, 1950) (Hydrozoa, Leptomedusae).

The mechanisms of strobilation have been studied in detail; many authors have reported parts of the strobilation-inducing cascade of *A. aurita* (Berking et al., 2005; Silverstone et al., 1977; Silverstone et al., 1978; Spangenberg, 1967; Spangenberg, 1971; Spangenberg, 1974; Fuchs et al., 2014). Fuchs and coworkers (2014) showed that the cascade consists of retinoic acid signaling that leads to the expression of the WSRRRWL peptide encoded by the strobilation-specific gene *CL390.* They also showed that five indole compounds induced strobilation of *A. aurita* immediately, and that the most effective indole compound, 5-methoxy-2-methylindole (5MeO2MeIn) induced strobilation of *Aurelia aurita* in two days. Also, Abrams et al. (2015) revealed that

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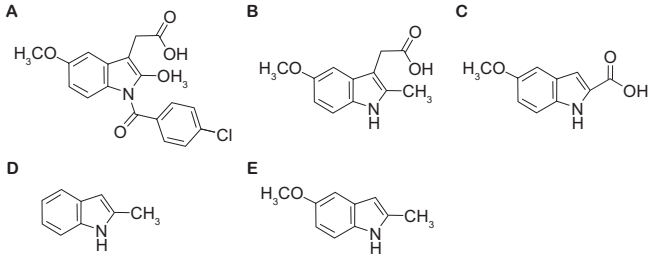


**Fig. 1.** Chemical structures of reagents used in the present experiments. **(A)** Indomethacin, **(B)** 5-methoxy-2-methyl-3-indoleacetic acid, **(C)** 5-methoxyindole-2-carboxylic acid, **(D)** 2-methylindole and **(E)** 5-methoxy-2-methylindole.

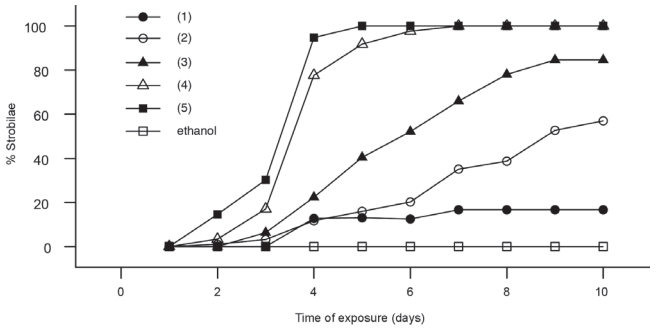


**Fig. 2.** Strobilation-inducing effect of five indole compounds on *Aurelia* sp. 1. (1) Indomethacin, (2) 5-methoxy-2-methyl-3-indoleacetic acid, (3) 5-methoxyindole-2-carboxylic acid, (4) 2-methylindole and (5) 5-Methoxy-2-methylindole. The assays were carried out four times using 24 polyps in each (total of 96 polyps for each reagent). 5-Methoxy-2-methylindole induced strobilation more effectively than the other reagents.

5MeO2MeIn induced strobilation of *Cotylorhiza tuberculata* in a week. However, whether the polyp-to-jellyfish transition of Cubozoa, Hydrozoa, or Scyphozoa other than *A. aurita* can be induced by indole compounds is unknown. To better understand the basic mechanism of metagenesis in Cnidaria, we need to examine the transition-inducing mechanism in Medusozoa. In the present study, we show that 5MeO2MeIn induces the polyp-to-jellyfish transition in Scyphozoa and Cubozoa, but not in Hydrozoa. This suggests that the basic induction systems of polyp-to-jellyfish transition are similar between Scyphozoa and Cubozoa.

## MATERIALS AND METHODS

### Preparation of reagents

The reagents tested in the present work were indomethacin (SIGMA, Tokyo, Japan) (Fig. 1A), 5-methoxy-2-methyl-3-indoleacetic acid (SIGMA, Fig. 1B), 5-methoxyindole-2-carboxylic acid (SIGMA, Fig. 1C), 2-methylindole (SIGMA, Fig. 1D) and 5-methoxy-2-methylindole (5MeO2MeIn, SIGMA, Fig. 1E). All reagents were prepared at 50 mM in ethanol and stored as stock solution at –20°C.

### Assay of five reagents' ability to induce polyp-to-jellyfish transition in *Aurelia* sp. 1

To assess the inducing ability of the aforementioned reagents, each was assayed in *Aurelia* sp. 1 (referred to in Schroth et al., 2002) from Yamagata prefecture, Japan. Polyps were cultured in artificial seawater (ASW) (REI-SEA, IWAKI, Tokyo, Japan) at 20 ± 2°C and fed newly hatched artemia twice per week. These were then placed in a 24-well microarray cassette (one polyp per well). The experimental solutions containing the different reagents at a concentration of 50 μM were deposited into each well (2 ml) on day 0, and the solution was replaced by fresh solution every day. Ethanol was used as a control. The number of polyps showing early signs of strobilation was

**Table 1.** Polyp-to-medusa transition inducing effect of 5-methoxy-2-methylindole in Medusozoa.

| Class | Order | Species | Number of transition (%)* | |
|---|---|---|---|---|
| | | | 5MeO2MeIn | Ethanol |
| Scyphozoa | Semaeostomeae | *Aurelia labiata* | 20 (100) | 0 (0) |
| | | *Aurelia limbata* | 20 (100) | 0 (0) |
| | | *Aurelia* sp. 1 | 20 (100) | 0 (0) |
| | | *Aurelia* sp. (purple Aurelia) | 20 (100) | 0 (0) |
| | | *Chrysaora achlyos* | 20 (100) | 0 (0) |
| | | *Chrysaora fuscescens* | 19 (95) | 0 (0) |
| | | *Chrysaora melanaster* | 20 (100) | 0 (0) |
| | | *Chrysaora pacifica* | 20 (100) | 0 (0) |
| | | *Chrysaora quinquecirrha* | 20 (100) | 0 (0) |
| | | *Cyanea capillata* | 20 (100) | 0 (0) |
| | | *Cyanea nozakii* | 20 (100) | 0 (0) |
| | | *Sanderia malayensis* | 20 (100) | 0 (0) |
| | | *Phacellophora camtschatica* | 0 (0) | 0 (0) |
| | Rhizostomeae | *Thysanostoma thysanura* | 20 (100) | 0 (0) |
| | | *Cotylorhiza tuberculata* | 20 (100) | 0 (0) |
| | | *Mastigias papua* | 10 (50) | 0 (0) |
| | | *Rhopilema esculentum* | 20 (100) | 0 (0) |
| Cubozoa | Carybdeida | *Carybdea marsupialis* | 20 (100) | 0 (0) |
| | | *Morbakka virulenta* | 20 (100) | 0 (0) |
| | | *Tripedalia binata* | 18 (90) | 0 (0) |
| | | *Tripedalia cystophora* | 14 (70) | 0 (0) |
| Hydrozoa | Leptothecata | *Aequorea coerulescens* | 0 (0) | 0 (0) |
| | | *Aequorea macrodactyla* | 0 (0) | 0 (0) |
| | | *Aequorea victoria* | 0 (0) | 0 (0) |
| | | *Eutonina indicans* | 0 (0) | 0 (0) |
| | | *Tima formosa* | 0 (0) | 0 (0) |
| | | *Laodicea undulata* | 0 (0) | 0 (0) |
| | | *Melicertum octocostatum* | 0 (0) | 0 (0) |
| | Anthoathecata | *Bougainvillia bitentaculata* | 0 (0) | 0 (0) |
| | | *Leuckartiara octona* | 0 (0) | 0 (0) |
| | | *Neoturris breviconis* | 0 (0) | 0 (0) |
| | | *Rathkea octopunctata* | 0 (0) | 0 (0) |
| | | *Sarsia tubulosa* | 0 (0) | 0 (0) |

*Number of polyps in which polyp-to-medusa transition was induced by 5-methoxy-2-methylindole (5MeO2MeIn) or ethanol after 10 days.

counted every day for 10 days. The appearance of a first constriction under the mouth was taken as an early sign of strobilation. The aforementioned process was carried out four times on four successive days.

**Assay of polyp-to-medusa transition induction by indole in 30 species of Medusozoa**

A total of 33 species were used in this experiment (17 in Scyphozoa, 4 in Cubozoa and 12 in Hydrozoa). Seventeen species of Scyphozoa, 1 of Cubozoa (*Carybdea marsupialis* (Linnaeus, 1758)) and 12 of Hydrozoa) were cultured in filtered natural sea water in Tsuruoka City Kamo Aquarium (Yamagata, Japan). The other three cubozoan polyps: *Morbakka virulenta* (Kishinouye, 1910), *Tripedalia binata* Moore, 1988 and *Tr. cystophora* Conant, 1897 were cultured in ASW. Polyps were cultured at the appropriate temperature for each species. *Aurelia limbata* (Brandt, 1835), *Chrysaora fuscescens* Brandt, 1835, *Eutonina indicans* (Romanes, 1876), *Melicertum octocostatum* (M. Sars, 1835), *Neoturris breviconis* (Murbach and Shearer, 1902), *Phacellophora camtschatica* Brandt, 1835, *Rathkea octopunctata* (M. Sars, 1835) and *Sarsia tubulosa* (M. Sars, 1835) were cultured at 5°C. *Aequorea coerulescens* (Brandt, 1835), *Au. labiata* Chamisso and Eysenhardt, 1821, *Aurelia* sp. from the coast of Columbia (customarily referred to "purple Aurelia"), *Ch. melanaster* Brandt, 1838, *Cyanea capillata* (Linnaeus, 1758) and *Laodicea undulata* (Forbes and Goodsir, 1853) were cultured at 10°C. *Aequorea victoria* (Murbach and Shearer, 1902), *Leuckartiara octona* (Fleming, 1823) and *Tima formosa* L. Agassiz, 1862 were cultured at 15°C. *Aequorea macrodactyla* (Brandt, 1835), *Aurelia* sp. 1, *Ch. achlyos* Martin et al., 1997, *Ch. pacifica* (Goette, 1886), *Ch. quinquecirrha* (Desor, 1848), *Cotylorhiza tuberculata* (Macri, 1778), *Mastigias papua* (Lesson, 1830), *Rhopilema esculentum* Kishinouye, 1891 (*R. asamushi* type) and *Mo. virulenta* were cultured at 20°C. *Bougainvillia bitentaculata* Uchida, 1925, *Ca. marsupialis*, *Cy. nozakii* Kishinouye, 1891, *Sanderia malayensis* Goette, 1886, *Thysanostoma thysanura* Haeckel, 1880, *Tr. binata* and *Tr. cystophora* were cultured at 25°C. For each species, 10 polyps (± 5 in Hydrozoa) were put into a 10-cm plastic Petri dish and cultured in 20 ml of testing solution containing 5MeO2MeIn at a concentration of 50 μM from the day 0. The culture solution was changed every day. Ethanol was used as a control. The number of polyps that showed early signs of the polyp-to-medusa transition was recorded every day for 10 days. This process was carried out twice, moving the starting date forward by one day. The appearance of a first constriction under the mouth was regarded as an early sign of polyp-to-medusa transition in Scyphozoa and Cubozoa, whereas the formation of medusa buds was regarded as an early sign of this transition in Hydrozoa. Polyps were fasted during the observation period.

## RESULTS

**Strobilation-inducing activity of five indole compounds**

We first tested the strobilation-inducing effect of five indole compounds on *Aurelia* sp. 1 as a function of days of induction (Fig. 2). 5MeO2MeIn was the fastest inducer, followed by 2-methylindole, 5-methoxyindole-2-carboxylic acid, 5-methoxy-2-methyl-3-indoleacetic acid and indomethacin. 5-methoxyindole-2-carboxylic acid, 5-methoxy-2-methyl-3-indoleacetic acid and indomethacin induced strobilation of some but not all polyps during the 10-days observation period.

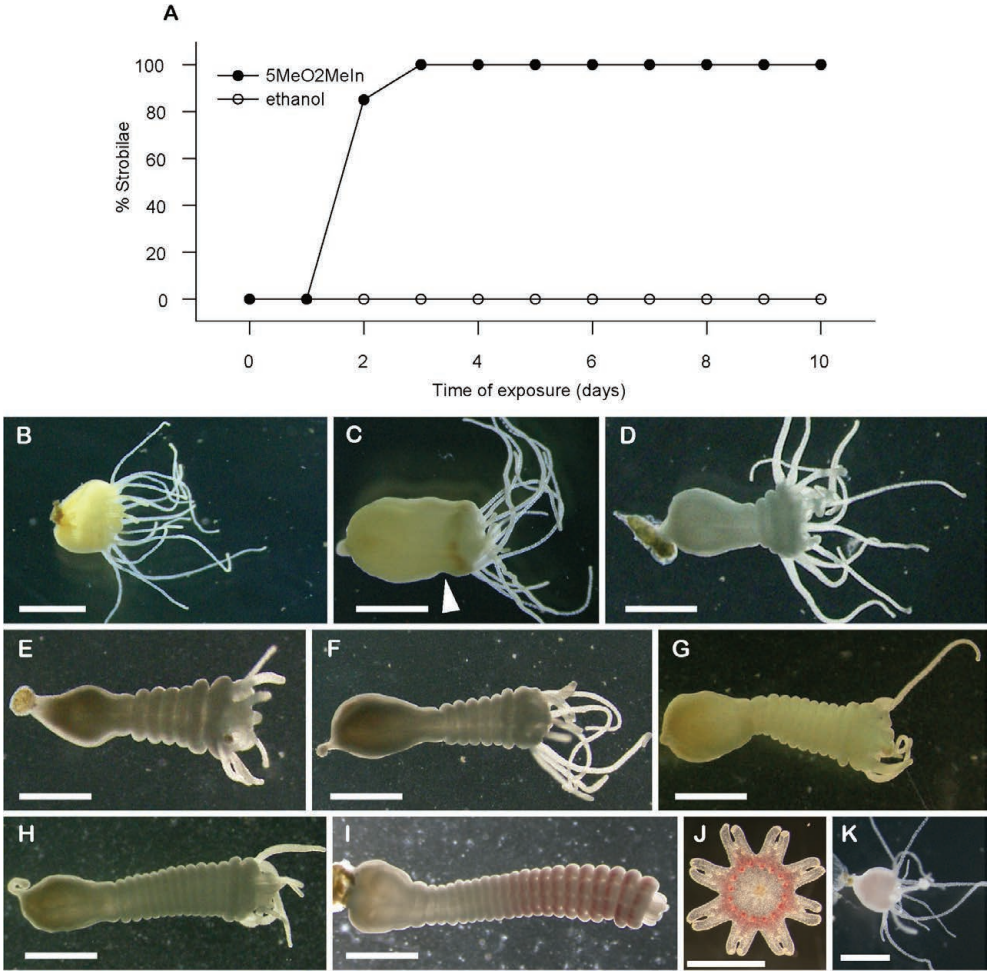


**Fig. 3.** Strobilation of *Chrysaora achlyos* initiated by 5-methoxy-2-methylindole (5MeO2MeIn). **(A)** Effect of 5MeO2MeIn on poly-discus strobilation of *Ch. achlyos*. The number of samples for each reagent was 20. **(B–I)** show the morphology of the strobilation process from days 1 to 8, respectively. On the second day, the polyp elongated and a constriction (arrowhead) appeared **(C)**. The number of constrictions increased with time **(D–H)**, and on the eighth day, the color of polyps turned purple **(I)**. Ephyra **(J)** started to swim off from strobila on the ninth day. Strobilation was not induced by ethanol even after 10 days **(K)**. The scale bar represents 1 mm.

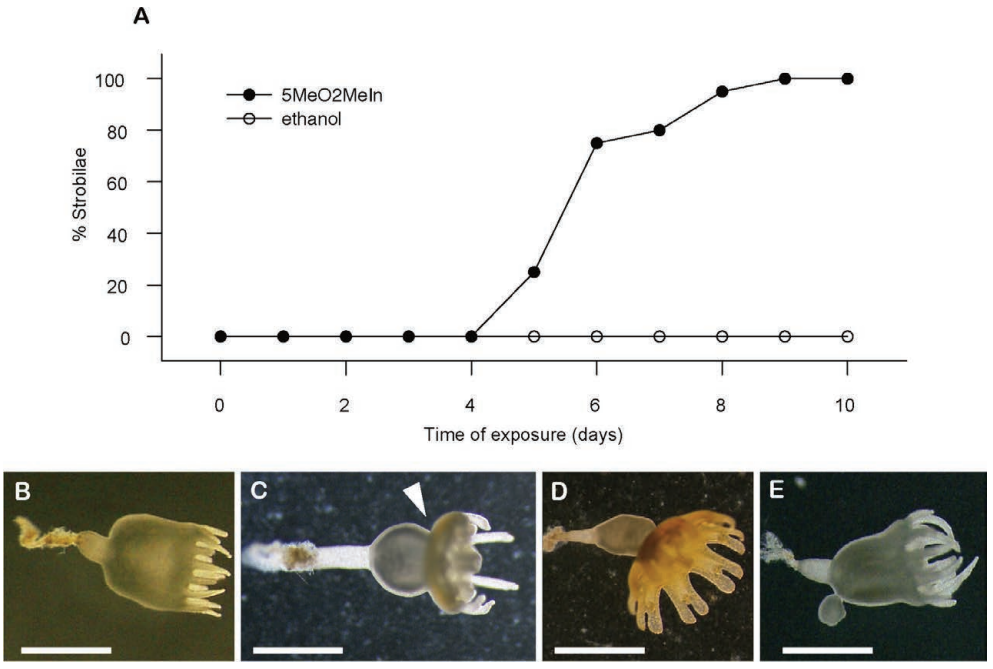


**Fig. 4.** Strobilation of *Thysanostoma thysanura* initiated by 5-methoxy-2-methylindole (5MeO2MeIn). **(A)** Effect of 5MeO2MeIn on the mono-discus strobilation of *Th. thysanura*. The number of samples for each reagent was 20. **(B–D)** show the morphology of the strobilation process on the first, fifth and tenth days, respectively. On the fifth day, a constriction (arrowhead) started to be formed **(C)**, and on the tenth day, an ephyra was formed on top of each polyp **(D)**. Strobilation was not induced by ethanol even after 10 days **(E)**. The scale bar represents 1 mm.

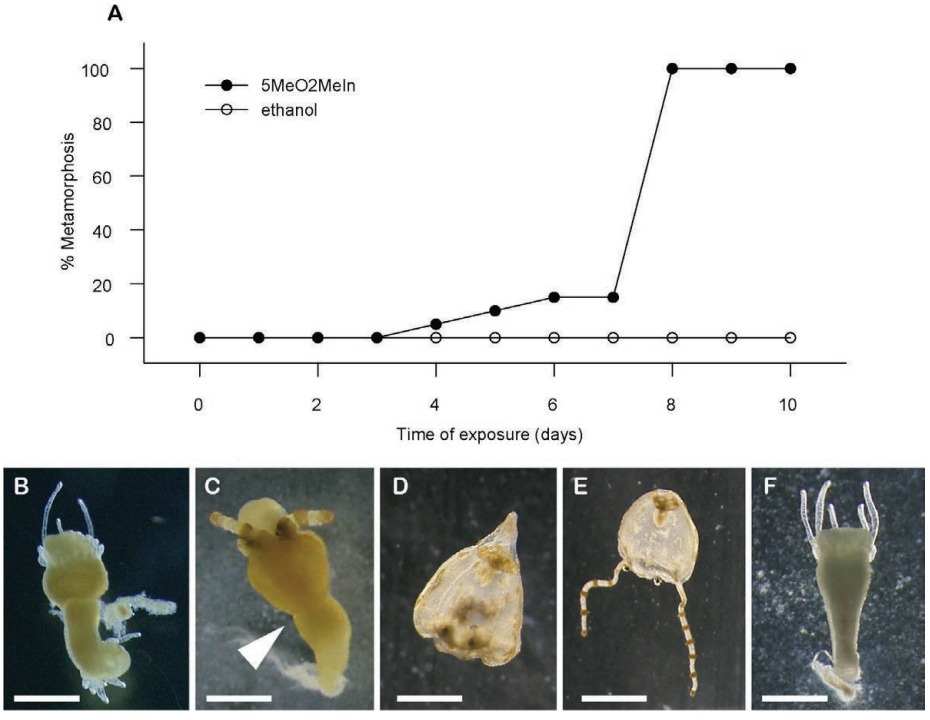


**Fig. 5.** Metamorphosis of *Carybdea marsupialis* initiated by 5-methoxy-2-methylindole. **(A)** Effect of 5MeO2MeIn on the metamorphosis of *Ca. marsupialis*. The number of samples for each reagent was 20. **(B)** and **(C)** show the morphology during the metamorphosis process on the first and fourth days, respectively. On the fourth day, the constriction (arrowhead) started to form. On the ninth day, the polyp metamorphosed into medusa with a protuberance on top of the bell **(D)**. The protuberance disappeared on the 10th day **(E)**. Ethanol did not induce metamorphosis **(F)**. The scale bar represents 1 mm.

### Strobilation-inducing ability in 33 Medusozoa species

The numbers of polyps that showed early signs of polyp-to-medusa transition during the 10-day observation period are shown in Table 1. In Scyphozoa, all species except for *P. camtschatica* showed signs of strobilation after the addition of 5MeO-2MeIn. In the case of *P. camtschatica*, the period of observation lasted up to 40 days, but there was no sign of strobilation. In Cubozoa, all species showed this sign of metamorphosis after the addition of 5MeO2MeIn. In contrast, none of the Hydrozoa species formed medusa buds. Thus, species that responded to 5MeO2MeIn were only found in Scyphozoa and Cubozoa.

Regarding the type of strobilation, three species in Rhizostomae (*T. thysanura*, *Cl. tuberculata* and *M. papua*) showed mono-discus strobilation, while the other 13 species of Scyphozoa, including one species in Rhizostomae, *R. esculentum* showed poly-discus strobilation. The daily increase in the number of strobilation-induced polyps and the strobilation process were then examined in a representative of each strobilation type: *T. thysanura* for the mono-discus strobilation type, *Cs. achlyos* for the poly-discus strobilation type and *Cd. marsupialis* for cubozoan metamorphosis (Figs. 3–5).

We first examined the effect of 5MeO2MeIn on the mono-discus strobilation of *T. thysanura* as a function of days of induction (Fig. 3A). The polyp showed no visible sign of strobilation (Fig. 3B), but a constriction (arrowhead) was observed on the fifth day (Fig. 3C). The number of polyps with a constriction increased gradually until the ninth day (Fig. 3A), and

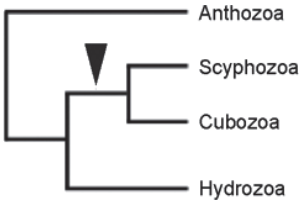


**Fig. 6.** Phylogenetic relationships of Scyphozoa, Cubozoa, and Hydrozoa (Modified from Collins, 2002; Zapata et al., 2015). The arrowhead shows the time point when common metamorphosis-inducing system which utilizes indole-based compounds appeared.

ephyra began to pulsate on the tenth day (Fig. 3D). The strobilation was not induced by ethanol (Fig. 3E). Next we examined the effect of 5MeO2MeIn on the poly-discus strobilation of *Cs. achlyos* as a function of days of induction (Fig. 4A). The polyp showed no visible sign of strobilation (Fig. 4B), but polyps elongated and the first constriction (arrowhead) was observed on the second day (Fig. 4C). The number of constrictions increased as strobilation progressed. Fig. 4 D–H show the morphology of strobilation from the third to the seventh day, respectively. On the eighth day, the color of strobila turned purple (Fig. 4I), and ephyra (Fig. 4J) started to swim off on the ninth day. The strobilation was not induced by ethanol (Fig. 4K). Finally, we examined the effect of 5MeO2MeIn on the metamorphosis of *Cd. marsupialis* as a function of days of induction (Fig. 5A). The polyp showed no visible sign of metamorphosis (Fig. 5B), but a constriction (arrowhead) was observed on the fourth day (Fig. 5C). The number of polyps with a constriction increased until the eighth day (Fig. 5A). On the ninth day, polyps metamorphosed into medusa with a protuberance on top of the bell (Fig. 5D), and this protuberance disappeared on the tenth day (Fig. 5E). The strobilation was not induced by ethanol (Fig. 5F).

## DISCUSSION

The polyp-to-medusa transition of Cnidaria is one of the most extensively studied examples of metagenesis among marine organisms. In *Aurelia aurita*, the transition from asexually reproducing benthic polyp to sexually reproducing planktonic medusa is termed strobilation. This process is regulated by a retinoic acid reaction cascade leading to the expression of a strobilation-specific gene, *CL390*, encoding the WSRRRWL peptide, which functions as a strobilation-inducing hormone (Fuchs et al., 2014). WSRRRWL peptide has two aromatic rings located in close proximity, the structure of which is similar to that of the anti-inflammatory drug indomethacin. Kuniyoshi and coworkers (2012) reported that indomethacin has the ability to induce strobilation in *Aurelia* sp. 1. Fuchs and coworkers (2014) also revealed that four indole compounds in addition to indomethacin had the ability to induce strobilation in *Au. aurita.* In their experiments, the strobilation-inducing ability varied among the five reagents, with 5-methoxy-2-methylindole (5MeO2MeIn) being the most effective. The same assay was conducted in *Aurelia* sp. 1 in the present study, and we found the same order of strobilation-inducing ability for these five reagents. This suggests that the responsiveness to these different reagents is conserved in closely related species.

The reagent 5MeO2MeIn was used in the strobilation-inducing assay in 33 species in Scyphozoa, Cubozoa and Hydrozoa. The results of that assay showed that 5MeO2MeIn induces strobilation in 16 of 17 scyphozoan species and metamorphosis in four cubozoan species tested (Table 1). This suggests that indole compounds induce polyp-to-medusa transition in Scyphozoa and Cubozoa irrespective of the type of transition. The fact that 5MeO2MeIn shares a common structure with the WSRRRWL peptide suggests that WSRRRWL peptide functions as a strobilation-inducing hormone in Scyphozoa and Cubozoa under natural conditions. Medusa budding was not induced by 5MeO2MeIn in any of 12 hydrozoan species in the present study, suggesting that indole-related hormones such as WSRRRWL peptide, would not function as medusa budding inducers in Hydrozoa. Together with the fact that Scyphozoa and Cubozoa are more closely related to each other than to Hydrozoa (Collins, 2002; Zapata et al., 2015), the present finding may suggest that the common ancestor of Scyphozoa and Cubozoa acquired the CL390 homologous protein after divergence from Hydrozoa (Fig. 6). However, 5MeO2MeIn did not induce strobilation in *Phacellophora camtschatica* (Scyphozoa, Semaeostomeae). *Phacellophora camtschatica* belongs to Phacellophoridae, which does not strictly conform to any other families in Semaeostomeae (Straehler et al., 2011), suggesting that the structure of CL390 homologous protein of *P. camtschatica* has changed during the course of evolution and does not share a common structure with 5MeO2MeIn. Further molecular biological studies, such as identification of the receptor of the polyp-to-jellyfish transition-inducing protein in Scyphozoa and Cubozoa, are needed to determine whether indole-related hormone functions as a metamorphosis hormone in Cnidaria.

Cnidaria is the most representative phylum in the animal kingdom that undergoes metagenesis. Metagenesis is a common life history strategy in the plant kingdom, while most animals do not undergo metagenesis. This may be because animals are able to migrate to different environments, and therefore it is more advantageous to develop sexual reproduction and produce offspring with new adaptations than to maintain asexual reproduction. In contrast, Cnidaria undergoes both sessile polyp generation, which increases the advantage of asexual reproduction, and medusa generation, which enables migration as well as new adaptations such as reproduction in other animals. Cnidaria has survived from the Ediacaran Era (Norris, 1989), and it is possible that one key to its robustness is its distinct metagenesis system. Further knowledge of the mechanism of induction of the polyp-to-jellyfish transition and the evolution of transition-inducing indole compounds will advance our understanding of the mechanisms of the metagenesis, a remarkable survival strategy of Cnidaria that has been lost in most animal phyla.

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## COMPETING INTERESTS

The authors have no competing interests to declare.

## AUTHOR CONTRIBUTIONS

LY designed and performing research, analyzed data. LY and HT wrote the paper. KO, CS and SI collected animals. HT obtained funding. All authors read and approved the final manuscript.

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