REVIEW

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New Perspectives on Semiconducting Conjugated Oligomers for Neuromodulation in *Hydra vulgaris*

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A general overview is provided on the neuromodulatory function of thiophene-based semiconductors discovered and characterized in the invertebrate model organism, the cnidarian *Hydra vulgaris*. The small freshwater polyp *Hydra* is an attractive animal model for neuromodulation due to its simple body anatomy and a nervous system with hundreds to thousands of neurons organized in distinct circuits, each controlling a limited set of behaviors. With the aim of characterizing the polymerization of the thiophene-based trimers in the soft tissues of this simple model, an unexpected animal behavior is observed in addition to polymerization, and the neurons involved and the possible underlying mechanisms are identified. To date, the neuromodulatory action of these compounds in other in vivo models has not been observed. Here, the recent data on the double function showed by thiophene-based trimers in *Hydra* is summarized, from the polymerization into conductive structures driven by endogenous enzymatic activities to neuromodulatory action on specific neuronal circuits. The data open intriguing research possibilities offered by this model organism in the field of organic bioelectronics for both neuromodulation and in situ production of conducting interfaces to influence biological processes and functions.

1. Introduction

Organic semiconductors are a class of π-conjugated molecules and polymers that have been widely exploited for optoelectronic devices and flexible circuits.[1] Over the past two decades, they have been investigated for developing biological interfaces as they have potential to improve the contact with the biological world.[2] One of their main advantages compared to inorganic semiconductors is the lack of native oxide that enables intimate connection with the biological milieu. Furthermore, their solution processability facilitates the development of interfaces with various form factors including thin, flexible and conformable devices that minimize tissue invasiveness or even 3D bioelectronics for mimicking the biological architecture.[3]

The physicochemical properties of organic semiconductors can be tuned via molecular design, while their electronic properties can be adjusted via molecular or electrochemical doping. Organic mixed ionic electronic conductors (OMIECs) are a subcategory of organic semiconductors. They are soft organic materials that solvate and transport ionic species as well as electronic charges, enabling an extensive ionic-electronic coupling. These materials can convert ionic signals into electronic readouts and, i.e., translating electronic signals into ionic/biochemical inputs.[4] Different characterization techniques are performed to reveal the structure of OMIECs, as well as to characterize the electrical and electrochemical aspects of the mixed transport and thus to guide the development of new materials.[5]

The ability of the electrolyte to percolate through the entire volume of the OMIEC film makes the capacitive coupling between ions and organic material volumetric rather than being limited to the film/electrolyte interface, with the ions stabilizing nearby electronic charges on the polymer backbone (e.g., polythiophene) through electrostatic interactions. This property ensures low impedance during recording and stimulation while minimizing faradaic processes responsible for changes in the chemical composition of the electrode and/or the electrolyte, as well as the formation of toxic products.[6–10]

OMIECs can be blends (heterogeneous systems) in which an ionic phase, such as a polyelectrolyte, is coupled with the conjugated polymer forming separated conducting microdomains (i.e., PEDOT:PSS). They can also be constituted of single components (homogeneous systems) in which the intimate proximity of the polymer chains and ions facilitates the

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electronic/ionic interaction and prevents the formation of conductive microdomains. Due to this characteristic, as well as their biocompatibility, enhanced conductivity without external dopants, and designable/tunable electronic properties, self-doped thiophenes have emerged as a valid alternative to heterogeneous polymers.[11,12] Recent studies have strategically focused on the copolymerization of monomers with different functionalization, including ionized or reactive functional groups, developing OMIECs with efficient electron and ion transport and the potential for post-functionalization, opening a new way for tailoring OMIECs propertiesto specific applications.[13]

The need for high-performing, conformable, and minimally invasive electrodes led to many novel strategies to achieve the seamless integration of OMIEC-based electrodes into living tissues, such as the chemical assembly of conductive interfaces in situ.[14] It has been recently showed that the water soluble thiophene-based monomer (2,5-bis(2,3-dihydrothieno[3,4-b][1,4]dioxin-5-yl) thiophene (ETE) backbone, functionalized on the central thiophene with a 4-ethoxybutane-1-sulfonic acid salt side chain (ETE-S), undergoes polymerization in plants[15–17] and in the freshwater polyp *Hydra*[18] due to the endogenous peroxidase enzymatic activity. Several other approaches have been reported to achieve the in vivo fabrication of OMIEC, based on chemical or genetic engineering and a variety of monomers.[14,19,20] However, while ETE-S polymerization in targeted tissues was evident (see paragraph 3), a question that remained unanswered and barely explored was whether the ETE-S trimer or other monomers undergoing in vivo assembly could induce any tissue response (from toxicity to degradation into smaller compounds) as they entered the biocatalytic machinery of the host tissues. In addition to these effects, when interacting with the nervous system, the exogenous organic interfaces, either in their polymeric or monomeric form, may also impact neuronal function, resulting in modulation of the animal behavior, making the evaluation of such issues even more urgent. Discovering the neuromodulatory properties of organic compounds and dissecting the targeted neuronal circuits is not easy especially in vertebrate, due to the complexity of the nervous system. Besides optogenetic approaches, behavioral studies may allow the correlation of neuronal activity to precise behaviors, and model organisms with simple nervous systems and limited behavioral repertoires may greatly help in this purpose. The coelenterate *Hydra vulgaris* represents an ideal model, due to a primitive neuronal net coordinating a small set of behaviors.[21–24] Pioneering this field, we have demonstrated that ETE-S can modulate *Hydra* behaviors and, in the longer term, it also undergoes an enzymatic polymerization producing living electronically conductive structures.[18,25] In the following sections, we will review and discuss ETE-S-induced behavioral response and in vivo polymerization in *Hydra*. We will also revisit the proposed neuromodulatory mechanism identified in *Hydra*[25] and provide some perspectives for a deeper comprehension of neuronal information processing.

1.1. Thiophene-Based Compounds

Thiophene-based trimers represent a new versatile class of compounds thanks to the large variety of functional groups that can be covalently bound to the thiophene ring. Their preparation involves a relatively simple synthesis using Suzuki coupling between 2,5-dibromo-3-thiophene hydroxyl and an EDOT boronic acid. This reaction leads to oligomers with an active hydroxyl group that can be easily modified with different side chains.[15,27,28] Starting from hydroxyethyl-thiophene, it was possible to obtain the Edot-Thiophene-Edot with the sulphonate group (ETE-S) and Edot-Thiophene-Edot with the trimethylammonium group (ETE-N), which have the same trimer backbone but different side chain, respectively a sulfonate group negatively charged or a trimethylammonium group positively charged. Starting from hydroxymethyl-EDOT, the trimer obtained is the Edot-Edot-Edot-Sulfonic group (EEE-S) with the same sulphonate side chain as ETE-S, and a pure EDOT, 3,4-ethylenedioxythiophene, trimer as backbone (**Figure 1**A).[15,29,30] The electronic properties and morphology of ETE-S oligomers were studied by a combination of theoretical and experimental tools. Spectroelectrochemistry revealed the efficient electrochemical doping of p(ETE-S) films, with the absorption maximum shifting from 550 nm for the de-doped state to 800 nm for the doped state. Electron paramagnetic resonance spectrometry (EPR) revealed that the charge carriers are bipolarons in the doped state. These experimental findings were supported by density functional theory (DFT) and time-dependent DFT calculations.[31,32] In another work, atomistic molecular dynamics simulations combined with Grazing Incidence Wide Angle X-Ray Scattering (GIWAXS), revealed that ETE-S oligomers form crystallites due to $\pi - \pi$ stacking. The simulations also revealed that percolative paths for the charge carriers are formed when the ETE-S oligomer length is at least two units.[33] These findings are supported by the high conductivity of $10 S/cm$ that was reported for the in vivo polymerized ETE-S in plants.[15,17] Thiophene trimers with charged side groups are water-soluble, making them suitable for interfacing with several biological entities.[25,27,28] In fact, it was demonstrated that terthiophenes exhibit various pharmacological activities, e.g., antibacterial,[34] antimicrobial,[35] antitumoral.[36] Similar to various aromatic-based compounds, they are naturally fluorescent and spontaneously cross the membrane of living cells, bounding to specific proteins inside live cells through non-covalent interactions. For these properties, they are used as colorimetric and fluorometric oligothiophene-based sensors.[37] Furthermore, thiophene derivates are also light and thermal transducers. The poly-3-hexylthiophene (P3HT), a thiophene-derivate polymer commonly used as active material in organic photovoltaics, could work as an electrophysiological sensor when interfaced with cultured excitable cells. After short visible pulsed light exposure, it could induce action potentials in primary rat hippocampal neurons,[6] restore light sensitivity in degenerated retinas explanted from albino rats, [38,39] and change the passive membrane properties in HEK-293 cells.[40] Moreover, the photothermal heating induced by these interfaces also increased the currents flowing through potassium inward rectifier channels, that regulate neuronal excitability,[41] and activated TRPV1 channels in human embryonic kidney cells.[42]

Interestingly, a light-mediated neuromodulatory effect was successfully obtained in the living organism *Hydra vulgaris* following the internalization and photostimulation of P3HT polymer nanoparticles into its tissues.[43] The results showed that P3HT-NPs photostimulation could modulate the animal

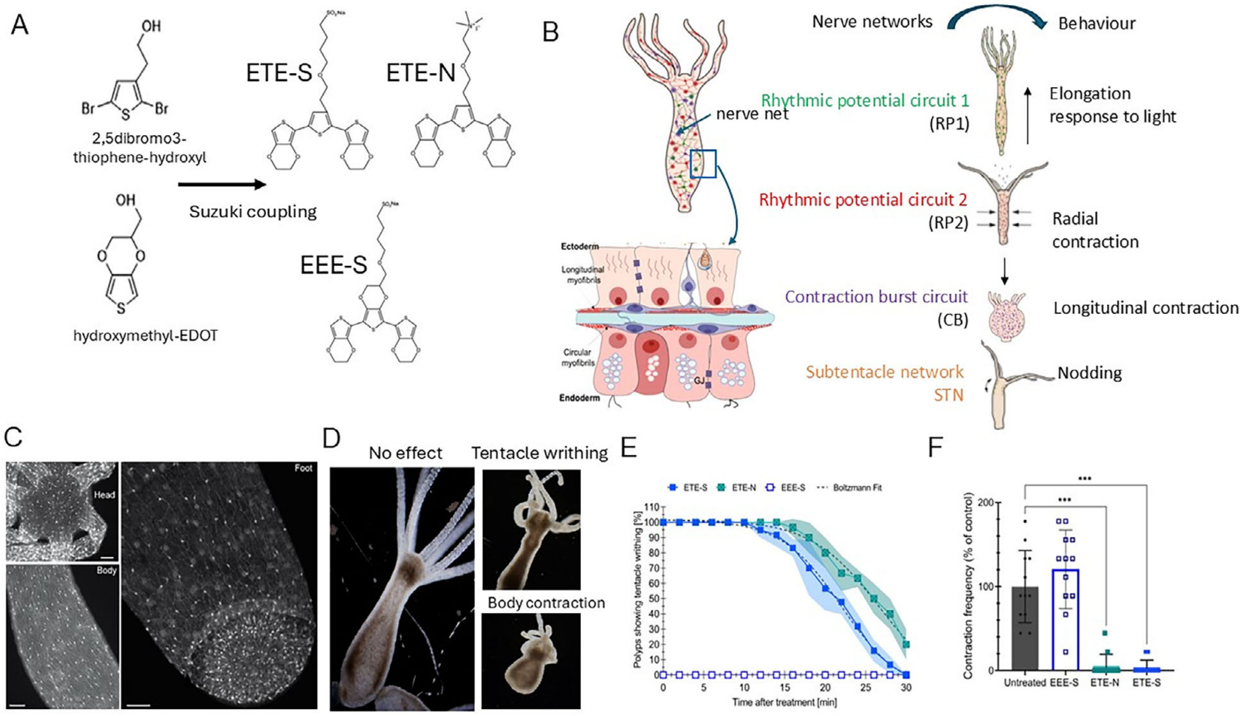

Figure 1. Semiconducting oligomers elicit specific behavioral responses in *Hydra vulgaris*. A) Molecular structure of the different EDOTbased trimers. B) *Hydra* polyp has a simple body structured as a bilayer composed of ectoderm and endoderm. Sensory and ganglial neurons are interspersed between the two layers, forming the *Hydra* nerve net (on the left, modified with permission from[25]) depicted as four non-overlapping neuronal subpopulations indicated in different colors (Adapted with permission from.[21] Copyright 2017, Elsevier). Each neural circuit is associated with a precise animal behavior and is depicted in diverse colors. C) An example of a neuronal circuit located on *Hydra* ectoderm. The circuit N3 extends from the foot to the tentacles. By calcium imaging, using genetically encoded calcium indicators (GCaMP), N3 neurons were associated with the *Hydra* elongation behavior. Reproduced with the permission from. Giez et al., 2023, bioRxiv, DOI: 10.1101/2023.09.15.557876. This work is licensed under a CC-BY-NC-ND 4.0 International license. D) Images of the tentacle writhing and contraction behaviors elicited in *Hydra* during feeding response or spontaneously, respectively. E) Temporal dynamic of the tentacle writhing induced by the three thiophene-based oligomers. F) Modulation of the spontaneous contraction/elongation events induced by the same trimers. For *Material and Methods* please, refer to Ref. [25].

behavior, i.e., the spontaneous body contractions, and induces the overexpression of genes involved in the light transduction pathway. Although eyeless, *Hydra* expresses various opsin-based pigments have been identified,[44] and the photomodulation of the animal periodic behavior has been largely demonstrated[45] together with a diurnal and circadian regulation,[46] offering a well-characterized system to screen photoactive materials. Interestingly, in addition to the behavioral response, the illumination of polyps treated with P3HT-NPs not only altered behavior but also enhanced the regeneration efficiency.[47] A boost in stem cell proliferation rate and a modulation of the redox species levels positively affected the animal regenerative and reproductive capabilities, confirming the possibility to optically control important cell functions through conducting polymer nanoparticles integrated into the tissue. These results showed the possibility to use *Hydra* in bioelectronics to screen biocompatibility, bioactivity and action mechanisms of semiconducting compounds.

1.2. *Hydra* as In vivo Model For Neuromodulation

One of the main challenges in the field of neuromodulation is the low availability of animal models suitable to test in vivo the bioactivity of compounds with neuroactive potential. Ideal animal models should easily enable the correlation between the test compound and behavioral modulation, which is intrinsically very hard in those animals, such as mammalian, characterized by complex behaviors and which nervous system is not easily accessible.

Hydra body is composed of two epithelial layers, ectoderm and endoderm, separated by an acellular matrix and a third lineage, the interstitial cell lineage, interspaced between them and giving rise to a few differentiated cell types, including the neurons. The nervous system, composed of hundreds to thousands of sensory neurons and ganglion cells, forms a nerve net extending along the entire body column and clustering only at the foot and head levels, which are considered putative integration points (Figure 1B).[24,45,48–52] The nerve net consists of a few independent sub-circuits, i.e., neuronal sub-population firing simultaneously, each controlling a precise animal behavior[22,23] such as longitudinal and radial contraction, elongation and nodding (Figure 1B). They are active synchronously in an oscillating manner and have been associated to extracellularly recorded electrical signals, e.g., contraction burst train (CB), consisting in a series of pulses (CPs) detected during animal longitudinal contractions, tentacle pulses (TPs) occurring during tentacle contractions, and rhythmic potentials (RPs) associated to radial contractions, all together characterizing the continuous periodic alternation of the animal.[21–23,45] The correlation between the activity of these neuronal circuits and the different behaviors induced by physiological or environmental conditions has been obtained by functional calcium imaging in *Hydra* transgenic strains expressing Ca^{2+} indicators in their neurons[21] and epithelial cells,[50,51] and is still object of ongoing investigations.

Furthermore, single-cell transcriptome analysis was employed to dissect at molecular level the differentiation trajectories of the nervous system from interstitial stem cell progenitors, enabling the assignment ofmolecular profiles to several neuronal circuits and their spatial distribution.[53,54] Thus, beside the three non-overlapping networks initially characterized,[21] four additional networks were identified, localized in diverse tissues and controlling single or multiple behaviors.[23,50,51,55,56]

The N3 cluster, for example, identified in RP1 ectodermal neurons, was related to locomotion behavior associated with elongation and to integration activity of the feeding state (Figure 1C). The N3 subpopulation also resulted unique in connecting and influencing other neuronal ectodermal populations (named N2, N6, N7) while counteracting the N1 cluster identified in CB ectodermal neurons.[26]

Ectodermal N6 neurons, characterized by sensory and ganglion cells at the tip and base of the head respectively, form a complex radial sub-network also connected to the N4 and N3 neurites of the head and differentially activated during mouth opening. Finally, N4 and N5 neurons, distributed only in the body column and head, appeared to belong to the RP2 endodermal network, associated with radial contractions during feeding and digestion behaviors.[21,26,51,52,57,58]

2. Neuroactive Properties of Organic Semiconducting Oligomers

In a recent study, we showed the biocompatibility of the ETE-S trimer in living *Hydra* and its ability to elicit precise behavioral responses[25] (Movies S1-S2; S7–S8) which consisted in the tentacle writhing (Figure 1D–E) associated to a strong inhibition of the spontaneous full-body elongation/contraction cycles (Figure 1F). These behaviors were found to be calcium-dependent, as they were strongly inhibited in Ca^{2+}-free solution, in the presence of EGTA or voltage-dependent calcium channel inhibitors (nifedipine), highlighting a fundamental role for Ca^{2+} as an intracellular intermediate in the cascade of events triggered by ETE oligomers (**Figure** 2A,B).

It must be noted that the tentacle writhing is a behavior usually elicited during the feeding response (i.e., in presence of live prey), or by the physiological activator of the feeding response, namely the glutathione (GSH). Interestingly, the GSH-induced tentacle writhing was not modulated by Ca^{2+} inhibitors (Figure 2C), suggesting that, despite the similarity in behavioral responses, distinct molecular pathways are triggered by different signals.

Hydra dissected heads were also responsive to ETE-S treatment, indicating head neurons as putative cellular targets of the ETE-S signal. Notably, while ETE-S could not modulate the rhythmic body contractions in decapitated bodies, amputated heads elicited a tentacle-writhing activity that lasted even longer than whole polyps (Figure 2D), suggesting a negative feedback control of the body neurons onto the animal behavior. Moreover, nerve-free polyps treated with ETE-S completely abolished both tentacle writhing and spontaneous contraction behavior while still exhibiting longitudinal contractions in response to mechanical pinching. This suggests that ETE-S triggers neuronal cells rather than acting on the contractile part (myofibrils) of epitheliomuscular cells[25] (Movies S6).

Electrophysiological recordings in treated polyps indicated that ETE-S also interfered with the *Hydra* electrical activity modifying the occurrence of CB trains (**Figure** 3A). Despite the inhibitory effect induced by ETE-S on the contraction behavior, the electrical profile showed a rise in the frequency of the CB events, and a consequent decrease in the IcBIs, i.e., the interval between two contraction trains.

Interestingly, another thiophene-based compound, EEE-S showed no modulatory action on tentacle writhing and contraction behavior, highlighting a crucial role played by the oligomer backbone in the neuromodulatory action. Even though ETE-S and EEE-S impacted differently on *Hydra* behavior (Figure 1E,F), electrophysiological recordings on EEE-S treated polyps (Figure 3A), revealed the same trend observed with ETE-S, i.e., a decrease in IcBIs.

These results, e.g., different behavioral responses despite a similar electrophysiological pattern, suggest that the two oligomers would actuate on different neuronal circuits and that their different structure could be the main determinant in the activation of specific neuronal subnet (Figure 3B). The emerging hypothesis is that the ETE-S oligomer, interacting with putative receptors located on sensory neurons, would positively affects the N3 sub-network (RP1), promoting the radial contraction, i.e., elongation, and disrupting the synergic interaction with the N1 subnet. To overcome the chronic elongation state, the tentacle contraction pulse (CPT) frequency would increase. Activation of the RP1 circuit would be also responsible for the tentacle writhing, as RP1 neurons have been shown to localize in tentacles.

Similarly, EEE-S oligomer would positively intervene on the N1 subnetwork, activating the CB neurons and inducing, in a direct manner, an increase in the CPT pattern frequency.

Further experiments are currently underway in our laboratory to explore additional compounds belonging to this class of semiconductive oligomers, to discover and define the potential of their neuromodulatory properties.

3. Future Perspectives for pETE-S Neuronal Integration in in vivo Models

The implementation of innovative polymerization procedures has made possible the use of OMIECs as building blocks for the formation of homogeneous conductive scaffolds that directly interface with biological systems, enhancing the transduction of the endogenous signaling in electronic signals and reducing the foreign body response.[59] However, the neuromodulatory effect of ETE-based compounds discovered in *Hydra* highlights the need for a detailed in vivo characterization of the effect of OMIECs monomers.

The group of Cui and Martin [60] first proposed the in situ electropolymerization in aqueous solution, a procedure that permits, by means of the applied potential, to induce the polymerization of

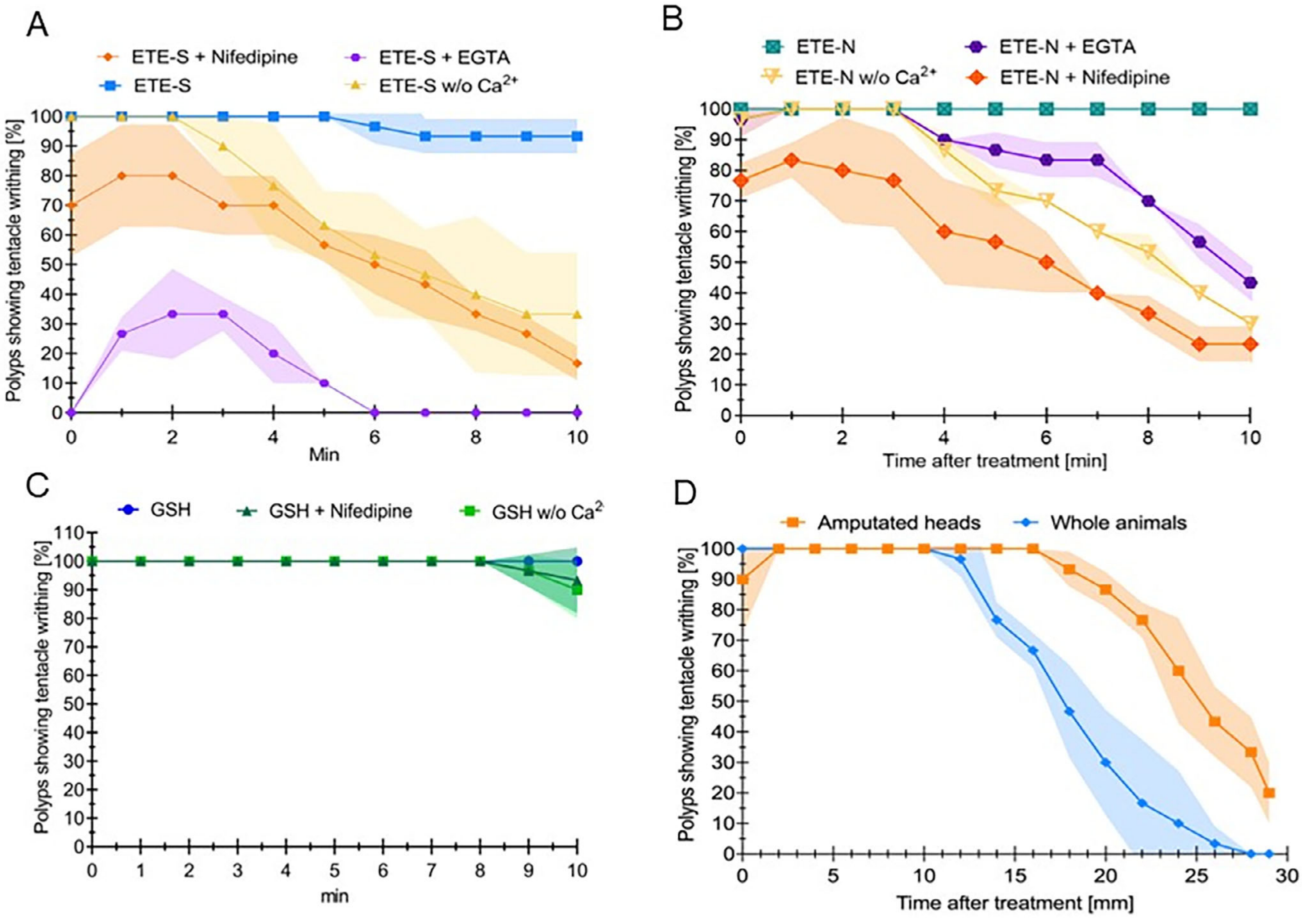

Figure 2. ETE-S and ETE-N induced behaviors are *Ca*$^{2+}$ dependent. Temporal dynamic of the tentacle writhing activity induced by A) ETE-S and B) ETE-N in the presence of Ca^{2+} inhibitors. The behavior is strongly inhibited by eliminating the Ca^{2+} from the medium or by blocking of Ca^{2+} channels, as indicated by the sharp decrease in the number of polyps showing tentacle writhing. C) Ca^{2+} modulation on the GSH-induced feeding response. The absence of Ca^{2+} does not affect the tentacle writhing behavior induced by GSH. D) ETE-S triggers head neurons. Amputated heads show an active tentacle writhing activity lasting even longer compared to whole animals. For *Material and Methods* please, refer to Ref. [25] and https://www.science.org/doi/10.1126/sciadv.adi5488 Supplementary information Movies S1–S8.

the oxidized monomer and to control the thickness of the polymer film which is the determinant factor in reducing the electrode impedance and improving its charge injection capability. In this case, the PEDOT film incorporated bioactive molecules to better promote cell adhesion and improve the intimate contact between nanoelectronics and cells. Later, it was demonstrated that, in presence of living neural cells,[14,61] EDOT could be safely electropolymerized around cultured neuronal cells resulting in a cell-templated, biomimetic conducting polymer matrix. Electropolymerization was also implemented in living mouse neural tissue, demonstrating that nano and micro-conducting PEDOT filaments extended and diffused out from the implanted electrodes and formed an electrically conductive network integrated within the living neural tissue.[14,61]

Currently, researchers are focusing their efforts in investigating the possibility to polymerize enzymatically conducting polymers directly within the living tissue in order to maximize their performance.

A more intimate coupling between tissue/probe was realized by Li et al. [62] that integrated EDOT polymerization with a 3D stretchable mesh of nanoelectronic components. When mixed to a growing human cardiac organoid, the cardiomyocyte electrical activity could be monitored throughout the whole development, showing optimal performance of the electronic device.

Another approach is represented by photosensitizer proteins (e.g., mini Singlet Oxygen Generator, miniSOG), i.e., oxidants able to induce more singlet oxygen than other reactive oxygen species (ROS). When genetically expressed in vitro in rat cortical neurons, they could assemble more efficiently conductive and/or insulating polymers on or within the neuronal membrane. Their optical control allowed precise modulation of the membrane capacitance and, in turn, neuron excitability.[63]

In mice infected wounds, the application of calcium alginate hydrogel pre-loaded with Horseradish peroxidase (HRP) promoted the biosynthesis of polyaniline derivative via the H_2O_2 overexpression induced by the bacterial growth. The near-infrared absorption properties of polyaniline also allowed a NIR control of the polymerization process. In fact, under NIR illumination, the bacterial growth was inhibited by a photothermal

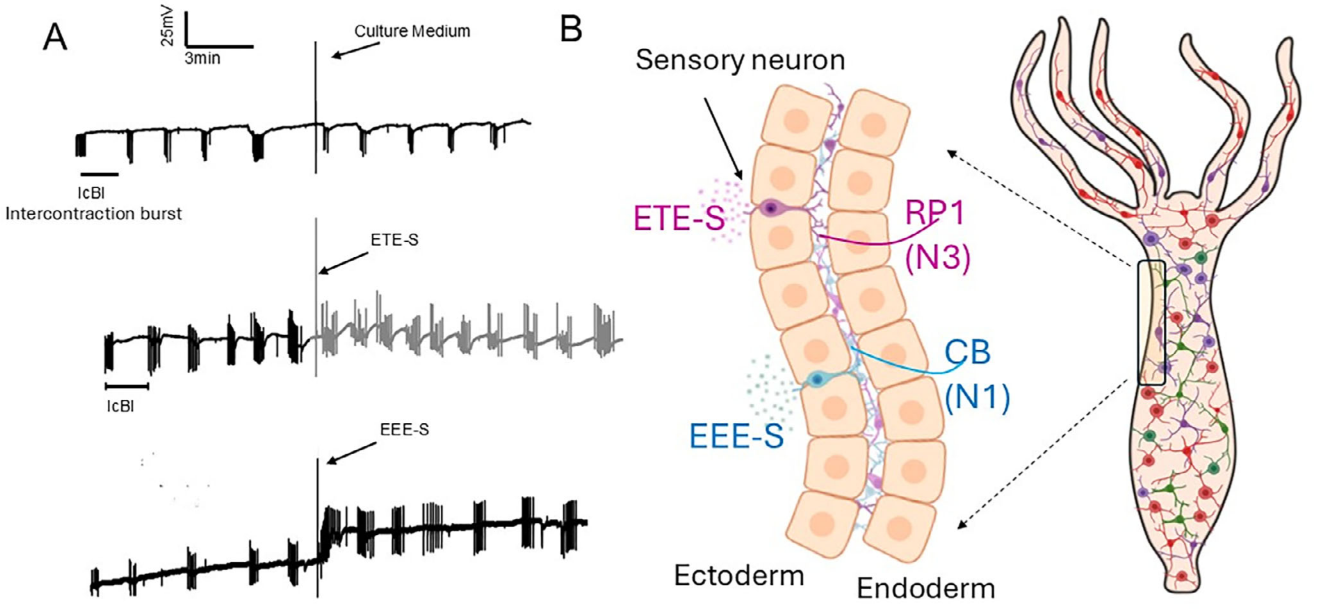

Figure 3. Neuromodulation of *Hydra* behaviors by thiophene-based trimers. A) The 20 min long recordings show an increased rhythmic activity measured as the time interval between two adjacent CB, i.e., intercontraction burst interval (IcBI). After 10 min of registration in non-treated *Hydra*, either the medium or ETE-S/EEE-S was added in the chamber (arrow) and registration continued for other 10 min. Both caused a decrease of the IcBI. B) Putative mechanism of the ETE-S and EEE-S on the *Hydra* neuronal ectodermal subnetworks. The enlarged inset shows two putative ectodermal subnetworks, the RP1 (N3) and CB (N1), possibly stimulated and supposed to be the neuronal net target of respectively, ETE-S and EEE-S oligomers, created with Biorender.com.[25]

effect, with a consequent reduction in ROS production and peroxidase activity.[64]

Light-responsive organic bilayers, i.e., based on *p*-type semiconductor polymers (hole transporting) and *n*-type dithiophene molecules (electron transporting), also could wirelessly trigger action potentials in primary cortical neuron cultures when exposed to low-intensity white light.[65]

In plants, a conformable multielectrode array based on organic electronics could register, with a high spatiotemporal resolution, the action potential propagation along the trap of the carnivorous plant *Venus flytrap*.[66] [67] demonstrated that within the vascular tissue of the plant stem, PEDOT-S, a self-doped PEDOT, self-organized and formed a homogeneous hydrogel conductor. In a later work, the same group showed that ETE-S aqueous solution could be uptaken by the vascular tissue of plant cuttings and polymerized within the entire xylem, even reaching the leaves and flowers.[15] They established that ETE-S polymerization was catalyzed by endogenous peroxidase enzyme in presence of physiological concentration of hydrogen peroxide that is necessary to activate the enzyme.[68] The activated enzyme formed radical trimers that could be combined to form dimers or longer oligomers via radical transfer. While their initial work focused on plant cutting, they also demonstrated electronic functionalization of the root system in intact plants without impacting the growth and development of the plant.[29] Later on, this capability was demonstrated in *Hydra*[18] driven by the endogenous peroxidase present in the animal foot. The process occurred spontaneously in a few hours, without the addition of H_2O_2, forming electrochemically active micrometer-sized domains, fully compatible with the survival of the animal and highly stable, as detached structures could be analyzed for weeks after their production (**Figure 4**). Due to their conducting properties, these self-organized polymeric structures may modulate the electrical behavior of the tissue seamlessly integrating OMIECs. This highlights the need to investigate by electrophysiological assays their impact on behavioral and neuronal processes.

In other organisms, such as the medicinal leeche (*Hirudo medicinalis*), and zebrafish (*Danio rerio*) in absence of endogenous enzymatic activity or key substrates, the polymerization of ETE-derivatives by peroxidase enzymes was demonstrated by exogenous injection at the nervous tissue interface of a mixture containing all constituents needed for polymerization of ETE-conducting polymer-gel.[19,69]

These findings confirm the possibility of in situ fabrication of conformable and conducting structures, paving the way for novel approaches in the field of the neurotechnologies. The possibility to genetically manipulate *Hydra* to express enzymatic activity in specific cells, i.e., neurons, envisages the production of neuromorphic electrical circuits. The achievements of these goals will allow us to investigate in vivo the contribution of different subnets to the information neuronal processing and to shed light on the influence that these conducting polymers exert on neural connectivity in this simple invertebrate.

4. Conclusion

We reviewed the dual function showed by a class of organic semiconducting compounds (ETE-based) in the small invertebrate *Hydra*. Beyond the spontaneous polymerization of these oligomers in *Hydra* cells expressing peroxidase activity, leading

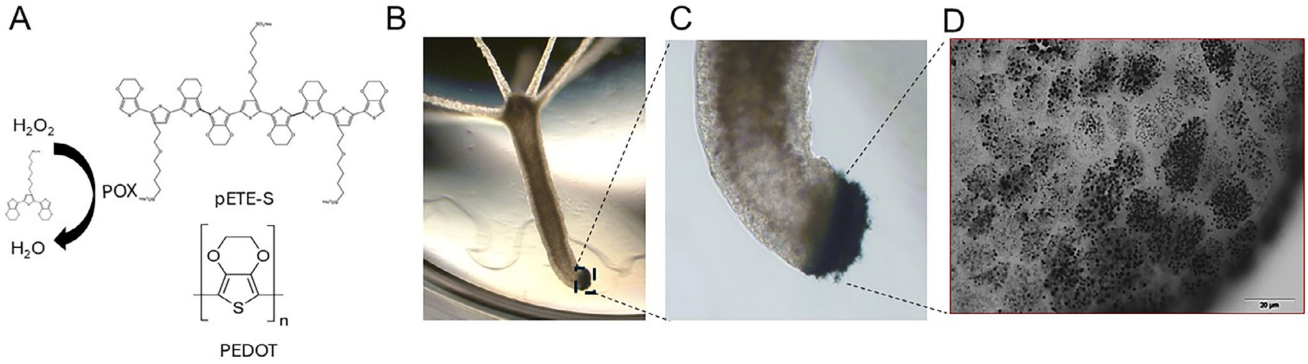

Figure 4. In vivo polymerization of pETE-S structures. A) Thiophene-based conducting polymers. B–D) Polymerization of ETE-S in *Hydra* basal disc cells, located into the animal foot. These cells express an high endogenous peroxidase activity into vesicles that, following ETE-S internalization, become black stained. The polymerization occurs in absence of exogenously applied H_2O_2. See Ref. [25] for further details.

to the in situ fabrication of conductive structures, we revealed their neuromodulatory function. Immediately after the animal exposure to ETE-S, two precise behaviors were elicited and found to depend on calcium and on neurons located on the animal head. Electrophysiological recordings further confirmed the ETE-oligomer activity on the contraction burst frequency and on two precise neuronal circuits. Overall, our studies open intriguing perspectives on the use of organic semiconductors to interface with the nervous system and, by revealing unexpected neuromodulatory effects played on a simple nerve net, they widen the field of applications of these compounds. Depending on the monomer/polymer configuration, they might be employed for cell-autonomous fabrication of living electronic devices (in their polymer form) and direct control of neuronal function in physiological and pathological contexts (monomer).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biopotentials, in vivo polymerization, *Hydra vulgaris*, neuromodulation, neuronal net, organic semiconductors (OSCs)

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