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Probing interactions of neurotransmitters with twin tailed anionic surfactant: A detailed physicochemical study

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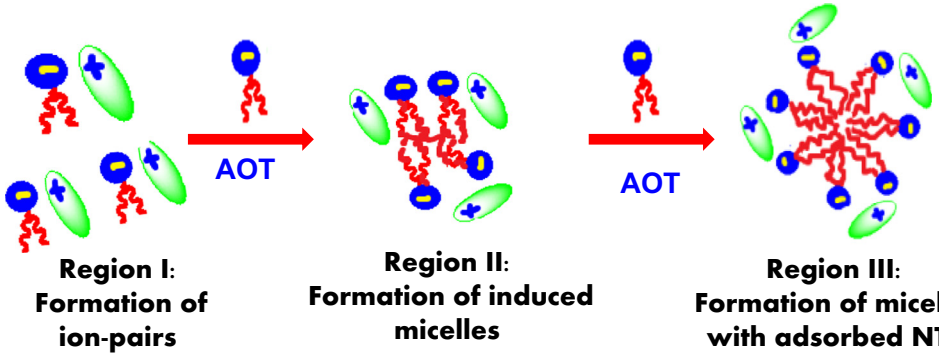
GRAPHICAL ABSTRACT



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ABSTRACT

Keeping in view the role of neurotransmitters (NTs) in central nervous system diseases and in controlling various physiological processes, present study is aimed to study the binding of neurotransmitters (NTs) such as norepinephrine hydrochloride (NE) and serotonin hydrochloride (5-HT) with twin tailed surfactant sodium bis(2-ethylhexyl)sulfosuccinate (AOT). Spectroscopic and electrochemical measurements combined with microcalorimetric measurements were used to characterize the interactions between AOT and NTs. Meteoric modifications to emission profile and absorption spectra of NTs upon addition of AOT are indicative of the binding of NTs with AOT. Distinct interactional states such as formation of ion-pairs, induced and regular micelles with adsorbed NTs molecules have been observed in different concentration regimes of AOT. The formation of ion-pairs from oppositely charged NTs and AOT is confirmed by the reduced absorbance, quenched fluorescence intensity and decrease in peak current (i_{pa}) as well as shifts in peak potential (E_{pa}) values. The stoichiometry and formation of the NTs–AOT complexes has been judged and the extent of interactions is quantitatively discussed in terms of binding constant (K) and free energy of binding (ΔG°). The enthalpy (ΔH°_{mic}) and free energy of micellization (ΔG°_{mic}) for AOT in presence and absence of NTs are determined from the enthalpy curves.

1. Introduction

Mental health issues are now more common in our society and is in the throes of a virtual epidemic of depression whose numbers are quite staggering. Major depressive disorder (MDD) is a

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common neuropsychiatric disorder characterized by continual pessimistic state leading to loss of interest or pleasure in normally enjoyable activities and increased mortality rates [1]. The psychosocial difficulties lead to impairments in social communication and up to 20% of the sufferers ultimately commit suicide [2]. The inadequate treatment of MDD and low response rate of all available antidepressant encourages research to develop novel methods to treat MDD.

Neurotransmitters (NTs) are a class of endogenous small chemical messenger compounds that transmit intercellular signals from a neuron to a target cell at chemical synapses in a process called the neurotransmission [3]. They have a systemic influence on the peripheral nervous system and are predominate actuators of the central nervous system (CNS). NTs are involved in broad range of brain functions such as mood, attention, reward processing, sleep, appetite, and cognition. The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of NTs such as serotonin (5-hydroxytryptamine; 5-HT), norepinephrine (NE) or dopamine in the central nervous system (CNS). Clinically effective antidepressant are those compounds that inhibits monoamine (5-HT, NE and dopamine) reuptake leading to their increased concentration in the synaptic cleft [4]. Thus, monitoring NTs levels and their metabolites is a vital tool to reveal the pathophysiology of depression and other neuropsychiatric disorders.

5-HT, the most extensively studied NT in depression, is a redox active biogenic monoamine NT, and is widely distributed in the brain making a significant contribution to brain functions. It plays a key role in numerous physiological processes, such as thermoregulation, liver regeneration, cardiovascular function and irritable bowel syndrome [5,6]. Serotonin receptor ligands are used for the treatment of a variety of disorders such as schizophrenia, depression, obesity, emesis [7]. A reduction in 5-HT concentration directs the development of depressive symptoms in subjects at increased risk of depression (MDD) and moreover an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency [8–10].

Norepinephrine (NE) is also an important neurotransmitter in the CNS, secreted by the adrenal medulla and plays numerous functions including regulation of the cardiovascular system, easing pain, sensing stress, depression and appetite [11,12]. It is used to treat myocardial infarction hypertension, bronchial asthma and heart disease. Alterations in plasma levels of NE may lead to many pathological conditions and diseases such as ganglion neuronal, ganglia neuroblastoma, paraganglioma and Parkinson' disease [13]. Almost all established antidepressants target the monoamine systems and inhibit the reuptake of both 5-HT and NE. Some powerful antidepressants such as selective serotonin reuptake inhibitor (SSRIs), tricyclic antidepressant (TCA), and monoamine oxidase (MAO) inhibitors have made indelible contributions [14]. However, some of them are of variable effectiveness and some exert undesirable side effects including decrease in bone mass and increased risk for osteoporosis and fewer show interactions with other drugs. Therefore, the development of alternative antidepressants is still the ideal aim tracked by researchers.

The knowledge of binding interactions between small molecules and macromolecules is a key to discover novel targets for drug development and are indispensable for the elucidation of their (patho-) physiological roles [15]. However due to the complex structure of biomembranes, the less intricate models such as surfactant aggregates having spherical structure have been used to mimic the biomembrane environments. Apart from allowing improved solubilization, micellar soft delivery systems offer a range of other advantages, including protection from enzymatic degradation, controlled drug release rate, protection from drug hydrolysis and reduction of toxicity, and increasing of bioavailability [16]. In the light of the above facts, it was thought worthwhile to undertake the study of interactions of the NTs regarded as drugs with micellar media. Our own research group has studied the interactions of surface active ionic liquids, such as 1-tetradecyl-3-methylimidazolium bromide (C14mimBr), with other neurotransmitters dopamine hydrochloride (DH) and acetylcholine chloride (AC) [17].

Now we are going to explore the interactions of NTs such as 5-HT and NE playing key role in MDD with sodium bis(2-ethylhexyl) sulfosuccinate (AOT), a twin-tailed surfactant. Literature survey reveals that extensive work has been done to study the binding interactions of drugs with surfactants but there is no report comprising the study of these NTs (neurotransmitters) with AOT or any other surfactant. The novelty of this report lies not only in the NTs selection procedure but in development of alternative to antidepressants in which directly NTs solubilized (or ion-pairs) in AOT micelles may be employed to increase the concentration of 5-HT or NE in the synaptic cleft. Moreover our present study is expected to contribute significantly to study bilayer–NT interactions in neural transmission [18].

AOT readily form vesicles in a dilute aqueous solution, is not only an excellent wetting agent but also an important material to simulate biological membranes [19]. AOT has been chosen in this study because it has low toxicity and can also be used as a pharmaceutical excipient [20]. Briefly, this paper takes into account a detailed analysis of interactions between AOT and NTs (NE and 5-HT) using spectroscopic techniques (UV–visible, fluorescence and three dimensional (3D) fluorescence), differential pulse voltammetric (DPV), and isothermal titration calorimetric (ITC) measurements. AOT and both NTs being oppositely charged interact electrostatically as well as hydrophobically to form ion pairs in addition to micelles with adsorbed NTs. Distinct interactional states such as formation of induced and regular micelles with adsorbed NTs molecules have been observed in different concentration regimes. The extent of interactions in these complexes is quantitatively discussed in the light of the binding constants. Our present study is expected to capture the interest of the scientific fraternity and the credit for this lies in the fact that depending upon the concentration of AOT, the behavior of NTs can be easily tuned. At low AOT concentrations they form ion-pairs called drug–surfactant catanionic mixture which can be employed in drug delivery. At high concentrations of AOT, NTs get solubilized in the micellar core thus mimicking the lipid–NTs interactions serving in neural transmission.

2. Experimental

2.1. Materials

Serotonin hydrochloride (5-hydroxytryptamine; 5-HT) and norepinephrine hydrochloride (NE) with stated purity >98% were procured from Fluka and sodium bis-2-ethylhexylsulfosuccinate (AOT) with purity >96% is product of Alfa-Aesar. All the chemicals were used without further purification.

All the stock solutions of NTs, and AOT were prepared in the 0.010 M phosphate buffer of pH = 7.4. NTs solutions were freshly prepared just before the experiments.

2.2. Methods

2.2.1. Spectroscopic measurements

Steady state fluorescence measurements were carried out by using F-4600 FL fluorescence spectrophotometer from Hitachi, Japan using a quartz cuvette having optical length of 10 mm at 298.15 ± 1 K. The intrinsic fluorescence of NE was monitored at