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Serotonin Discharge Regulation by Additional Neurotransmitters of Rat Hippocampus Associated With the Continence Central Circuit

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Purpose: The lower urinary tract is believed to be centrally regulated with the involvement of a range of neurotransmitters. The parasympathetic excitatory input to the urinary bladder is suppressed when the serotonergic system is activated, and thereby voiding is blocked. In healthy people, continence is usually underpinned by hippocampal formation (circuit 3). In order to advance knowledge of how serotonergic neurons and additional nerve fibers were correlated, the purpose of the present work was to research how the discharge of serotonin from hippocampal slices was affected by different neurotransmitters in rat models.

Methods: The adopted procedure involved administration of the central neurotransmitters acetylcholine, norepinephrine, dopamine, N-methyl-D-aspartate (NMDA), gamma-aminobutyric acid (GABA), glycine, and neuropeptide Y as well as monitoring of the alterations in the discharge of [³H]5-hydroxytryptamine (5-HT). Furthermore, to determine whether the effect of the neurotransmitters was influenced by interneuron, tetrodotoxin was also employed.

Results: Acetylcholine (10⁻²M) did not alter [³H]5-HT discharge, whereas more 5-HT was discharged from the hippocampal slices of rats under stimulation by norepinephrine (10⁻³M) as well as dopamine (10⁻³M) and tetrodotoxin (10⁻⁵M) did not inhibit the discharge. By contrast, tetrodotoxin inhibited the discharge of [³H]5-HT that was exacerbated by NMDA (10⁻⁴M). Meanwhile, compared to control, GABA (10⁻³M), glycine (10⁻³M), or neuropeptide Y (10⁻⁴M) did not alter the [³H]5-HT discharge.

Conclusions: From the research findings, it can be concluded that 5-HT discharge from rat hippocampus is enhanced by norepinephrine and dopamine through direct effect on the 5-HT neuronal terminal. By contrast, 5-HT discharge is intensified by NMDA by activating interneurons.

Keywords: Serotonin; Hippocampal slices; N-methyl-D-aspartate; Norepinephrine; Dopamine

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• Conflict of Interest: No potential conflict of interest relevant to this article was reported.

HIGHLIGHTS
• A range of different neurons was involved in 5-HT discharge from rat hippocampal slices.
• 5-HT discharge was intensified by norepinephrine and dopamine through direct action on the 5-HT neuronal terminal.
• 5-HT discharge was intensified by NMDA in an indirect manner, via interneuron mediation.

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INTRODUCTION

The lower urinary tract is thought to be centrally regulated by different neurotransmitters. Evidence suggests that the spinal and supraspinal reflex pathways controlling the bladder and external urethral sphincter are dependent on the neurotransmitter glutamate, which exerts its effect on both \textit{N}-methyl-\textit{D}-aspartate (NMDA) and non-NMDA receptors. Meanwhile, the activated receptor type, the site where the receptors are found in the brain, and the species are the determinants of the effect (inhibition or excitation) of certain neurotransmitters, including dopamine and acetylcholine (Ach). Tonic suppressive regulation is presented by inhibitory amino acids gamma-aminobutyric acid (GABA) and glycine within the pontine micturition center (PMC), modulating the capacity of the bladder [1-3].

A major neurotransmitter that blocks central control is serotonin (5-hydroxytryptamine, 5-HT). Serotonergic innervation of high density characterizes the spinal reflex circuits with a role in the voiding activity. Voiding can be inhibited when the central serotonergic system is activated as this blocks the parasympathetic excitatory input to the urinary bladder. Furthermore, thoracic sympathetic preganglionic neurons are activated long term by 5-HT. Research on cats has shown that reflex bladder activity is suppressed when the raphe nuclei are stimulated. Furthermore, the sacral parasympathetic nucleus contains 5-HT1A and 5-HT2 receptors. Cat micturition is suppressed when 5-HT1A receptors are activated whereas rat micturition is unaffected [4-6]. Serotonergic neurons are present in medullary raphe nuclei, which are among the brain neurons that participate in the regulation of the bladder, urethra, and urethral sphincter [7]. Nevertheless, knowledge is limited regarding the network of different neurotransmitters involved in the central regulation of serotonin.

Sacral preganglionic neurons or the area of the sacral dorsal commissure are supplied directly with synaptic inputs by neurons in PMC. These neurons are considered to play a significant role in facilitating the effect of excitation or suppression on voiding or continence [8]. In healthy people, the gradual filling of the bladder is usually accompanied by the activation of the subcortical network, including the periaquiductal gray and parahippocampal cortex, with no sensation (circuit 3). It seems that this process occurs without the participation of the cortical areas. The circuit is especially related to the safety emotional facets of voiding given the nearness of the parahippocampal cortex to the amygdala. More specifically, the circuit may use the presumed safe signal of continence from the hypothalamus to deliver output to the brainstem nuclei [5,9]. Extensive research has been conducted on the internal and external links of nerve cells in the hippocampus.

Regarding the manner in which the nerves are distributed within the hippocampus, the locus coeruleus and the raphe nuclei are respectively the entry points for the noradrenergic nerve fibers and the serotonergic nerve fibers. The majority of the hippocampal regions, particularly the dentate gyrus, are traversed by these 2 types of nerve fibers. Furthermore, the hippocampus also includes dopaminergic nerve fibers from the ventral tegmental region, while the medial septal nucleus is the source of the cholinergic nerve fibers, GABAergic nerve fiber, and glutaminergic nerve fibers entering the hippocampus. Moreover, the dentate gyrus, hippocampal CA1, subiculum, and the polymorphic layers of the entorhinal cortex all contain the neuropeptide Y [10,11].

Fiber-derived neurotransmitters are capable of modulating the discharge of additional neurotransmitters. Serotonin discharge from serotonergic nerve fibers originating in raphe nuclei or corpus striatum was diminished by glutamate, while suppression of glutamate prevented such an effect. Furthermore, both tetrodotoxin and bicuculline, a suppressor of GABA, inhibited glutamate from reducing 5-HT. This led to the proposition that GABA interneuron exerted negative modulation of 5-HT discharge from the serotonergic nerve fiber terminal in rat hippocampus [12].

To comprehend the action of the micturition-regulating central circuits and the manner in which they can be modulated to manage bladder dysfunction, it is necessary to understand the neurochemical signals in these circuits. On this basis, it may be possible to devise new pharmacological treatment interventions.

In the context of the brain slices isolated empirically, there is clear understanding of how hippocampal neurons are synaptically connected and the \textit{in vivo} qualities displayed by such connections, with strict control of temperature, oxygen pressure, and pH. For these reasons, hippocampal slices are good materials for experiments [13]. The way in which the unplanned discharge of 5-HT from the hippocampal slices of rats was influenced by a number of neurotransmitters was documented in the present work. Moreover, to explore interneuron participation, the impact of tetrodotoxin on the effect of the neurotransmitters was analyzed as well.
MATERIALS AND METHODS

Hippocampal Slice Preparation
All study protocols were performed in keeping with the National Institute of Health Guide for the Care and Use of Laboratory Animals (2001); they were sanctioned by the facility’s Institutional Animal Care and Use Committee.

The empirical work employed Sprague-Dawley rats of adult age and male sex and weighing 150–200 g. They were acclimatized to laboratory conditions for a minimum of one week. After decapitation, the extraction of the brain of every rat was conducted quickly. The brain was separated into its 2 halves at midline. A McIlwain mechanical tissue chopper (The Mickle Laboratory Engineering Co., Gomshall, Surrey, UK) was used for 400-μm transverse slicing of the hippocampus from both brain halves. Each one of these processes was carried out on ice and ice-cold (2°C–4°C) standard incubation medium. The composition of the standard incubation medium included 124mM of NaCl, 4mM of KCl, 2mM of CaCl2, 1mM of MgSO4, 1.25mM of KH2PO4, 25mM of NaHCO3, and 10mM of glucose, with a pH of 7.3–7.5 and 95% O2/5% CO2. The metabolic degeneration of 5-HT was avoided through the addition of 12.5 μm of nialamide (Sigma Chemical Co., St. Louis, MO, USA).

Empirical Procedure
To reach equilibrium, 6 hippocampal slices from the rats were kept in standard incubation medium with a temperature of 37°C and 95% O2/5% CO2 saturation for half an hour. This was followed by substitution of the incubation medium with fresh medium comprising [3H]5-HT (0.1μM, 74μCi; Amersham International plc., Buckinghamshire, UK) for uptake. The slices were incubated for 20 minutes and then washed thrice with standard incubation medium. The next step was arbitrary separation of the slices and transfer to 6 glass vials with a volume of incubation medium of 3 mL. Re-uptake all through the experiment was prevented through the addition of 10 μm of zimelidine (Packard Instrument Company Inc., Downers Grove, IL, USA) to the medium. The content of every vial was removed and an identical amount of new medium was added every 10 minutes for a period of 100 minutes. The removed content helped to measure how radioactive the discharged [3H]5-HT was. The initial 50 minutes of the procedure were followed by the administration of the testing pharmaceutical agents at the sixth and seventh 10-minute intervals, respectively. Administration of tetrodotoxin was done all through the experiment (0–100 minutes).

Measurement of [3H]5-HT Radioactivity
A mixture was produced from 1 mL of medium removed from vial at 10-minute intervals and 9 mL of liquid scintillation cocktail (READY SAFE, Beckman Instruments Inc., Fullerton, CA, USA). A liquid scintillation counter (Beckman Instruments Inc.) was employed to measure the mixture radioactivity. Furthermore, 1 mL of tissue solubilizer (SOLUENE, Packard Instrument Co., Inc., Downers Grove, IL, USA) was applied to the tissues, followed by 2-hour incubation at 37°C in order to determine how radioactive the [3H]5-HT remaining on the hippocampal slices was. The tissue solubilizer was subsequently neutralized through addition of 70 μL of glacial acetic acid (Merk & Co., Inc., Kenilworth, NJ, USA). Moreover, for measurement purposes, a mixture was created from 100 μL of the fully solubilized specimen and 9 mL of liquid scintillation cocktail.

Pharmaceutical Agents
Sigma Chemical Co. supplied the Ach, norepinephrine, dopamine, NMDA, GABA, glycine, neuropeptide Y, tetrodotoxin, and nialamide, while Amersham International plc. and Research Biochemicals International respectively supplied [3H]5-hydroxytryptamine and zimelidine HCl. Packard Instrument Company Inc. (Downers Grove, IL, USA) supplied the tissue solubilizer Soluene 350 and Beckman Instruments Inc. (Downers Grove, IL, USA) supplied the liquid scintillation cocktail Ready Safe.

Analysis of Data
The expression of every result took the form of fractional release. The applied definition of fractional release (FR) was:

\[
FR(\%) = \frac{cpm (medium) FR \times 100}{cpm (medium) TL + cpm (tissue)}
\]

Cpm (medium) FR denoted the radioactivity (counts per min, cpm) of [3H]5-HT discharged into the media collected during the specified interval of 10 minutes; cpm (medium) TL denoted the totality of the radioactivity (cpm) of [3H]5-HT discharged into the media collected at 10-minute intervals from the established time fraction to the final point of the period of observation; and cpm (tissue) denoted the radioactivity (cpm) of [3H]5-HT lefton hippocampal slices following the period of observation of 100 minutes.
Analysis of variances with subsequent Scheffe test was conducted to statistically compare the different groups, with the significance level being established at 0.05.

RESULTS

The Discharge of [3H]5-HT in Control Group and Group With Prior Administration of Tetrodotoxin in Conditions of Standard Media

5-HT was discharged spontaneously from the slices of hippocampus all through the empirical work. The initial 40 minutes saw a fast reduction in the discharge of 5-HT, followed by stable discharge until the end of the observation period (100 minutes). Furthermore, the unplanned 5-HT discharge was unaffected by tetrodotoxin (10⁻⁶ M) administration, while the administration of the pharmaceutical agents was done for 20 minutes at the sixth and seventh 10-minute intervals. The chosen datum point was the discharge of 5-HT at the fifth 10-minute interval and the expression of alterations in the discharge took the form of percent values contrasted against the fifth 10-minute interval (Fig. 1).

Norepinephrine- or Dopamine-Induced Alteration in [3H]5-HT Discharge

Norepinephrine and dopamine were employed to investigate how the unplanned discharge of 5-HT from the slices of hippocampus was affected by the adrenergic action.

By comparison to control, norepinephrine (10⁻⁶ M) induced a markedly higher discharge of 5-HT at both the sixth 10-minute interval (115.7% ± 2.3%) and the seventh 10-minute interval (105.8% ± 5.5%) (P < 0.05). Similarly, more 5-HT was discharged from the slices of hippocampus under the action of dopamine. In fact, as shown in Fig. 2, dopamine elicited a more intense discharge of 5-HT compared to norepinephrine. Additionally, the discharge of 5-HT remained at a heightened level for an extra 20 minutes following dopamine removal from the incubation medium.

The action of norepinephrine and dopamine was analyzed following tetrodotoxin (10⁻⁶ M) administration in order to determine if interneuron involvement was the reason why norepinephrine or dopamine enhanced 5-HT discharge. It was thus found that 5-HT discharge from hippocampal slices triggered by norepinephrine and dopamine was unaffected by tetrodotoxin (Figs. 2 and 3).

NMDA-Induced Alteration in [3H]5-HT Discharge

The action of NMDA was investigated to assess the glutamergic impact on the unplanned discharge of 5-HT from the slices of hippocampus. As illustrated in Fig. 2, compared to control, NMDA (10⁻⁴ M) induced a markedly higher discharge of 5-HT after both 10 minutes of treatment (122.5 ± 2.4%) and after 20 minutes of treatment (105.0 ± 3.4%) (P < 0.05). However, the

Fig. 1. The impact of tetrodotoxin on the unplanned discharge (cpm) of 5-hydroxytryptamine (5-HT) from the hippocampal slices of rats. Administration of tetrodotoxin continued all through the empirical work. In the initial 40 minutes, there was a fast reduction in 5-HT discharge, while subsequently 5-HT discharge became stable up to 100 minutes. TTX, tetrodotoxin.
NMDA-induced rise in 5-HT discharge was inhibited when tetrodotoxin (10^-6M) treatment was applied before NMDA administration (P < 0.05) (Figs. 2, 3).

**Ach-Induced Alteration in [³H]5-HT Discharge**

Ach treatment was applied to the incubation medium for 20 minutes to determine how 5-HT discharge from the slices of hippocampus was affected by the cholinergic neurotransmitter. The control group exhibited [³H]5-HT discharge of 94.9% ± 1.0% at the sixth 10-minute interval and 92.3% ± 1.1% at the seventh 10-minute interval. As shown in Fig. 4, the [³H]5-HT discharge from hippocampal slices was unaffected by Ach (10^-6M) administration.

**[³H]5-HT Discharge Alteration Induced by GABA, Glycine, or Neuropeptide Y**

Analysis was also conducted on the influence of the amino acid neurotransmitters GABA and glycine and the peptide neurotransmitter neuropeptide Y on the unplanned discharge of 5-HT from rat hippocampal slices. Results indicated that those neurotransmitters had no effect on the discharge (Fig. 4).
DISCUSSION

The upper medulla or pons is the main location where ca
thecholaminergic neurons are found. Micturition is regulated
with the involvement of the spinal noradrenergic system, which
blocks afferent input from the bladder and promotes enhanced
bladder contractility by mediating the descending limb of the
spinal micturition reflex [14,15]. Micturition is suppressed by
dopamine via D1-like receptors and stimulated via D2-like re
ceptors [16]. Entering from the locus coeruleus, noradrener
ergic nerve fibers alongside serotonergic nerve fibers traverse
most of the hippocampus, particularly the dentate gyrus. Fur
thermore, the hippocampus and subiculum contain dopami
nergic nerve fibers from the ventral segmental region. The
present work discovered that norepinephrine and dopamine
differed markedly regarding 5-HT discharge [15,16].

By comparison to control, both the norepinephrine (10^{-5}M)

group and the dopamine (10^{-5}M) group differed markedly in
terms of 5-HT discharge. This supported the conclusion that
5-HT discharge could be influenced by norepinephrine or do
pamine. Furthermore, by comparison to norepinephrine, dopa
mine induced the discharge of more 5-HT, therefore having a
greater influence (Fig. 2). What is more, prior administration of
tetrodotoxin did not inhibit the enhanced 5-HT discharge from
the slices of hippocampus triggered by either norepinephrine or
dopamine. Therefore, it was deduced that the serotonergic
erve fiber terminals were impacted by the noradrenaliner
and dopaminergic nerve fibers in a direct manner, without in
terneuron mediation (Fig. 3).

It is considered that glutamate is the main neurotransmitter
in Barrington nucleus neurons innervation the preganglionic
parasympathetic neurons that cause the detrusors to contract
[1,3]. Furthermore, it seems that glutamate serves as excitatory
transmitter in the supraspinal pathway that regulates micturi
tion. Alongside interneurons and fibers stemming from the
medulla oblongata, glutamate occurs within the terminals of
primary afferent neurons in the spinal cord. NMDA receptors
are among the different subtypes of receptors through which

Exerting its effect via the NMDA receptor, the excitatory ami
no acid neurotransmitter glutamate was observed in this work
to impact 5-HT discharge from the terminal of serotonergic
nerve fibers [17].

By comparison to control, the group admin
istered NMDA (10^{-4}M) exhibited higher 5-HT discharge
from rat hippocampal slices, leading to the conclusion that
5-HT discharge regulation may depend on NMDA. Mean
time, as shown in Fig. 3, the rise in 5-HT discharge from hip
pocampal slices was inhibited in the context of prior adminis
tration of tetrodotoxin. Therefore, 5-HT discharge from rat
 hippocampal slices is influenced by the excitatory amino acid
neurotransmitter NMDA, which acts via interneuron media

tion rather than straight on the glutamatergic nerve terminals.

The micturition reflex in the spinal cord is suppressed by
muscarinic Ach receptors. Meanwhile, it has been observed
that the rat micturition reflex is stimulated by nicotine admin
istered intrathecaly, meaning that the voiding function is regu
lated with the participation of nicotinic receptors [18]. As illus
trated in Fig. 4, the present work revealed that the Ach (10^{-5}M)
group and the control group did not differ markedly in terms of
5-HT discharge, implying that the serotonergic nerve fiber is
not influenced by the cholinergic nerve fiber.

The dentate gyrus, hippocampus, and subiculum make up the
hippocampal formation. Immunoreactive cells with sensi

Fig. 4. The impact of acetylcholine, gamma-aminobutyric acid
(GABA), glycine or neuropeptide Y on 5-hydroxytryptamine
(5-HT) discharge from rat hippocampal slices. The expression
of every point takes the form of a percentage of the value at 50
minutes. Administration of the target pharmaceutical agents
was done at the sixth and seventh 10-minute interval following
the initial 50 minutes of the period of observation. 5-HT dis
charge was not enhanced by acetylcholine, GABA, glycine, or
neuropeptide Y comparison to control of the sixth (60 min) and
seven 10-minute intervals (70 min). Expression of values takes
the form of mean ± standard error of the mean.
Fig. 5. The involvement of different additional neurotransmitters in 5-hydroxytryptamine (5-HT) discharge from the hippocampal slices of rats. 5-HT discharge is enhanced by norepinephrine and dopamine through direct action on the 5-HT neuronal terminal. Meanwhile, 5-HT discharge is indirectly enhanced by NMDA via interneuron mediation. GABA, gamma-aminobutyric acid; NPY, neuropeptide Y; Gly, glycine; Glu, glutamate; DA, dopamine; NE, norepinephrine; Ach, acetylcholine; NMDA, N-methyl-D-aspartate; X, no effect on the discharge.

Neuronal regulatory mechanisms underpinning bladder function depend significantly on glycinergic and GABAergic interneurons. Both the micturition reflex and glutamatergic neurons are suppressed by glycinergic and GABAergic branches to the lumbosacral cord [21]. The present work observed that, by comparison to control, 5-HT discharge from hippocampal slices was more or less the same in the groups administered the inhibitory amino acid neurotransmitters GABA (10^{-5}M) or glycine (10^{-5}M) found within hippocampal formation interneurons (Fig. 4). Similar findings were obtained regarding the peptide neurotransmitter neuropeptide Y (10^{-5}M) as well (Fig. 4). This led to the conclusion that 5-HT discharge was not regulated by GABA, glycine, or neuropeptide Y via interneuron mediation.

By contrast to Ach, GABA, glycine, and neuropeptide Y, the results indicated that norepinephrine, DOPA, and NMDA influenced 5-HT discharge from the hippocampus (Fig. 5).

In conclusion, the current work defended the premise that a range of different neurons was involved in 5-HT discharge from rat hippocampal slices. More specifically, 5-HT discharge was intensified by norepinephrine and dopamine through direct action on the 5-HT neuronal terminal. Meanwhile, 5-HT discharge was intensified by NMDA in an indirect manner, via interneuron mediation.

AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: YSS
- Data curation: JHK, YSA
- Formal analysis: YSA, YSS
- Funding acquisition: YSS
Methodology: JHK, YSA
Project administration: YSS
Visualization: YSA
Writing-original draft: JHK, YSS
Writing-review & editing: YSA, YSS

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