Journal club

## From discovery to function: The similarities and differences of neuromodulators



Chen Jie Sun Mengshi Jiang Xinyu

2018.11.30



## From discovery to function: The similarities and differences of neuromodulators

> Neurotransmitter: The classical chemical messenger

> Neurohormone: A hormone that is produced by neurosecretory cells

> Neuropeptide: The small protein-like molecules



## Neurotransmitter: The classical chemical messenger

Chen Jie

## The discovery of neurotransmitter

Popularize

Popularize

**Reticular theory**: **Everything in the nervous** system, such as brain, is a single continuous network

The majority of synaptic communication in the brain was electrical

**Neuron doctrine:** The nervous system is made up of discrete individual cells

Camillo Golgi





Discover

May, 1888

A 20 to 40 nm gap between neurons (known today as the synaptic cleft)

Suggested communication via

synaptic cleft

chemical messengers traversing the

Awarded the Nobel Prize in 1906, A pioneer of modern neuroscience

From wikipedia

### Acetylcholine: the first identified neurotransmitter



## What Defines a Neurotransmitter?

- 1. The substance must be present within the presynaptic neuron.
- 2. The substance must be released in response to presynaptic depolarization, and the release must be Ca2+-dependent.
- 3. Specific receptors for the substance must be present on the postsynaptic cell.

![](_page_5_Figure_4.jpeg)

Neuroscience. 3rd edition

## **Categories of Neurotransmitters**

![](_page_6_Figure_1.jpeg)

## Neurotransmitters Receptors

> Ionotropic receptors

#### Metabotropic receptors(G-protein-coupled receptors)

![](_page_7_Figure_3.jpeg)

Neuroscience. 3rd edition

### Neurotransmitters Receptors

#### Table 3–3: Ionotropic and metabotropic neurotransmitter receptors encoded by the human genome

Nourotronomittor	lonot	ropic	Metabotropic		
Neurotransmitter	Name Number of genes		Name	Number of genes	
Acetylcholine	nicotinic ACh receptor	16	muscarinic ACh receptor	5	
	NMDA receptor	7	matabatrania dutamata	8	
Glutamate	AMPA receptor	4	receptor (mGluR)		
	others	7			
GABA	GABA <sub>A</sub> receptor	19	GABA <sub>B</sub> receptor	2	
Glycine	glycine receptor	5			
ATP	P2X receptor	7	P2Y receptor	8	
Serotonin (5-HT)	5-HT <sub>3</sub> receptor	5	5-HT <sub>1, 2, 4, 6, 7</sub> receptors	13	
Dopamine			dopamine receptor	5	
			α-adrenergic receptor	6	
Norepineprinie (epineprinie)			β-adrenergic receptor	3	
Histamine			histamine receptor	4	
Adenosine			adenosine receptor	3	
Neuropeptides			neuropeptide receptors	dozens	

### Neurotransmitters and Behaviors

## ——A case study of dopamine

## Basic information of dopamine

Dopamine was first synthesized in 1910 by George Barger and James

Ewens

- First identified in the human brain by Kathleen Montagu in 1957
- ➢ Dopamine's function as a

neurotransmitter was first recognized in 1958 by Arvid Carlsson and Nils-Åke Hillarp

![](_page_10_Figure_6.jpeg)

Dopamine

 $-CH_2 - CH_2 - \dot{N}H_3$ 

## Searching related papers

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	Abstract		•	Contains	•	dopamine				
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	Joffe. M. E.: Turn	2018	(	senetic loss of GluN2B in D	1-e	xpressing cell t		Neuropsychop	2018/11	Journal Article

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	Jois, S.; Chan, Y	20:	Confir	m Online Search				Front Physiol	2018/11	Journal Article
	Sun, F.; Lei, Y.; Y	20:	Foun	nd 24797 records.				Mol Psychiatry	2018/11	Journal Article
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	Wendler, E.; de S	20:						Prog Neuropsy	2018/11	Journal Article
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## Searching related papers based on review

![](_page_12_Figure_1.jpeg)

![](_page_13_Figure_2.jpeg)

#### **Dopamine regulates sleep and arousal in** *Drosophila*

![](_page_13_Figure_4.jpeg)

Optogenetic stimulation of dopaminergic neurons silences dFB neurons and promotes awakening

Taro Ueno et al, 2012

Diogo Pimentel et al, 2016

Innate behavior

#### Increased dopamine level enhances male-male courtship in Drosophila

![](_page_14_Figure_3.jpeg)

VMAT: Vesicular monoamine transporters

А

![](_page_14_Figure_6.jpeg)

![](_page_14_Figure_7.jpeg)

Tong Liu et al.2008

H-Y Chang et al. 2006

Innate behavior

#### **Dopaminergic Modulation of Sucrose Acceptance Behavior in Drosophila**

Hunger and DA Increase the Sugar Sensitivity of the PER

![](_page_15_Figure_4.jpeg)

Hidehiko K. Inagaki et al.2012

![](_page_15_Figure_6.jpeg)

Sunanda Marella et al.2012

Learning and Memory

![](_page_16_Figure_2.jpeg)

•, Wild-type flies after training with positive reinforcement;  $\blacksquare$ , Df/+ flies after positive reinforcement;  $\Box$ , Df/+ flies after negative reinforcement;  $\Box$ , Df/+ flies after negative reinforcement.

BRUCE L. TEMPEL et al. 1984

Block with TH or NP5272 driver significantly impairs aversive memory

Yoshinori Aso et al. 2010

#### **Dopamine and Octopamine Differentiate between Aversive and Appetitive Memories in** *Drosophila*

![](_page_17_Figure_3.jpeg)

Scott Waddell 2010

#### In mammal

Proc. Natl. Acad. Sci. USA Vol. 85, pp. 5274–5278, July 1988 Neurobiology

#### Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats

![](_page_18_Figure_4.jpeg)

#### The effect of abused substances on human ventral striatal dopamine release

### Time:

Studying *in vivo* dopamine function in humans became possible in the mid-1990s

### Method:

Radiotracer imaging techniques, such as <sup>11</sup>C-raclopride positron emission tomography (PET) and <sup>123</sup>I-iodobenzamide (IBZM) single-photon emission computed tomography (SPECT)

![](_page_19_Figure_7.jpeg)

![](_page_19_Figure_8.jpeg)

In mammal

#### Dopamine and Reward Prediction Error (RPE)

![](_page_20_Figure_3.jpeg)

CS: conditioned stimulus

Mitsuko Watabe-Uchida et al. 2017

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## Neurohormone: a hormone that is produced by neurosecretory cells

Sun Mengshi

#### The first endocrine experiment: Berthold's experiment in 1849

![](_page_24_Figure_1.jpeg)

![](_page_24_Figure_2.jpeg)

![](_page_25_Picture_0.jpeg)

Ernest Starling British physiologist, 1866-1927

#### The Nobel Prize in Physiology or Medicine 1950

![](_page_25_Picture_3.jpeg)

Photo from the Nobel Foundation archive.

Edward Calvin Kendall Prize share: 1/3

archive. **Tadeus Reichstein** Prize share: 1/3

Photo from the Nobel Foundation

![](_page_25_Picture_7.jpeg)

Photo from the Nobel Foundation archive.

**Philip Showalter** Hench Prize share: 1/3

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#### f science has vn how the a new word can for research...

EMBO reports VOL 6 | NO 6 | 2005

Tata, J. 2005. One hundred years of hormones. EMBO reports. 6, 6 (2005), 490-496

#### Neuroendocrinology

![](_page_26_Picture_1.jpeg)

A multidisciplinary subject on the interaction between the brain and endocrine system and the influence of this interaction on the behavior of animals and humans.

The first neuroendocrine factors to be identified:

thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH).

![](_page_26_Picture_5.jpeg)

Ernst Scharrer (August 1, 1905 - April 29, 1965) Berta Scharrer (December 1, 1906 - July 23, 1995)

#### Hormone:

![](_page_27_Figure_1.jpeg)

Reece, Jane B., et al. Campbell Biology. Tenth edition. Boston: Pearson, 2014. I. Raven, Peter H, et al. Biology. Ninth edition. McGraw-Hill, 2011.

Response

Response

#### Hormones differ in structure and solubility

![](_page_28_Figure_1.jpeg)

Hydrophilic

Hormones are eventually destroyed by their target cells or cleared from the blood by the liver or the kidney.

Reece, Jane B., et al. *Campbell Biology*. Seventh edition. Boston: Pearson, 2014.I. Raven, Peter H, et al. *Biology*. Ninth edition. McGraw-Hill, 2011.

Lipophilic

1. Hormones

![](_page_29_Figure_0.jpeg)

Figure 45.2a-c, Reece, Jane B., et al. Campbell Biology. Seventh edition. Boston: Pearson, 2014.

A case study of drosophila insulin-like peptide (Dilp)

The discovery of drosophila insulin-like peptide:

A specific, high-affinity insulin-binding protein. The first insulin receptor dInR. (Petruzzelli L et al. 1985)

genomic or EST sequencing and bioinformatic data mining

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DILP1-7 (Brogiolo et al., 2001)
```

genetic screen

```
DILP 8 ( Colombani J, 2012, Garelli A, 2012)
```

![](_page_30_Picture_7.jpeg)

Two relaxin receptor-like GPCRs for DILP (Van Hiel MB,2015) Lgr3 (CG31096) is the ligand of the relaxin-like DILP8. (Colombani J,2015)

Diop, S. and Bodmer, R. 2015

#### □ Anatomy and organization of insulin producing cells( IPCs)

![](_page_31_Figure_1.jpeg)

CC: Corpora cardiaca

Dilp1: in larval IPCs (by *in situ* hybridization) Dilp6: predominantly expressed in the fat body (by Quantitative RT–PCR) Dilp8: Ovary

Rulifson et al. 2002, Hua Bai, et al.2012,

![](_page_31_Figure_5.jpeg)

https://droso4schools.wordpress.com/organs/

![](_page_31_Figure_7.jpeg)

#### **D** Parcital functional roles of IPCs and DILPs

• Lifespan and stress

![](_page_32_Figure_2.jpeg)

Broughton, S. et al. 2005, 2008

![](_page_33_Figure_0.jpeg)

Adult fat body *dilp6* expression represses *dilp2* and *dilp5* mRNA in the brain, and the secretion of DILP2 into the hemolymph

Hua Bai, et al.2012,

Conserved nutrient signaling pathways that regulate longevity

![](_page_34_Figure_1.jpeg)

Fat accumulation, antioxidant enzyme SOD (e a decrease in the free radical superoxide), HSPs (protection of proteins by chaperones), autophagy, translation...

Fontana, L. et al. 2010.

![](_page_35_Figure_0.jpeg)

The insulin hormone carries information about the metabolic state (for example, whether it is starving or well-fed) throughout the whole animal.

Ko, K. et al. 2015. Susy M. Kim . et al .2017

#### • Reproductive behavior

![](_page_36_Figure_1.jpeg)

Insulin signaling in female Drosophila links diet and sexual attractiveness

![](_page_36_Figure_3.jpeg)

an enzyme that is responsible for female pheromone synthesis

Lin, W.-S. et al. 2018

![](_page_37_Figure_0.jpeg)

#### Insulin Signaling Regulates Female Sexual Receptivity during Starvation in Drosophila

Lebreton, S. et al. 2017.

**Sleep and Locomotor activity** ٠

Regulation of Sleep by Insulin-like Peptide System in *Drosophila melanogaster* Cong, X. et al. 2015.

stress

Attraction towards noxious food

![](_page_38_Figure_2.jpeg)

#### **Extrinsic regulators of insulin-like peptide output in** *Drosophila*.

![](_page_39_Figure_1.jpeg)

Fat body senses the the circulating glucose and amino acid levels, then convey the signals to IPCs in the brain. AstA, DH31 are signals from midgut.

5-HT1A receptors are expressed in IPCs.

etc.

Only metabotropic GABA<sub>B</sub> receptor and UPD2 inactivates GABAergic neurons.

Knockdown the OAMB in IPCs altered sleep-wake pattern.

Lst are CC-cell-derived decretin hormone that suppresses by high-sugar feeding.

Alfa, R. and Kim, S. 2016. Nässel, D. et al. 2013.

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## Neuropeptide:the small protein-like signaling molecules ——A case study of neuropeptide F

Jiang Xinyu

## Substance P is the earliest discovered neuropeptide in 1931

![](_page_43_Picture_1.jpeg)

### AN UNIDENTIFIED DEPRESSOR SUBSTANCE IN CERTAIN TISSUE EXTRACTS.

BY U. S. V. EULER AND J. H. GADDUM.

(From the National Institute for Medical Research, Hampstead, London, N.W. 3.)

![](_page_43_Picture_5.jpeg)

DEPRESSOR SUBSTANCES IN EXTRACTS OF INTESTINE.

BY J. H. GADDUM AND H. SCHILD.

(From the National Institute for Medical Research, London, N.W. 3.)

(Received July 9, 1934.)

### ACTH was first discovered to affect behavior in 1953

![](_page_44_Figure_1.jpeg)

Mirsky, I.A., Miller, R. (1953)

## The concept of neuropeptide was first proposed by De Wied in 1969

![](_page_45_Picture_1.jpeg)

## Neuropeptides

They are short chains of amino acids that are active in the nervous system. In some cases they transmit signals between nerve cells and also serve the body as a hormone

## The development path of neuropeptide

![](_page_46_Figure_1.jpeg)

## Thus the factor is revealed as a neuropeptide

## Neuropeptide classification by location

Category	Name			
Brain-gut peptides	Glucagon、Neuropeptide Y、Substance P、 Neurotensin			
Pituitary hormones	ACTH、MSH、Oxytocin、Vasopressin			
Hypothalamic releasing factors	CRH、GRH、TRH			
Opioid peptides	Endorphin, Enkephalin, Dynophin			
Other peptides	Angiotensin, CGRP			

Eric, J. N., Steven, E (2009)

## The biosynthesis and metabolism of neuropeptide

![](_page_48_Figure_1.jpeg)

#### Synthetic site: Soma

It requires cleavage of propeptide to form many different bioactive neuropeptides.

#### • Storage site: LDCV

Neuropeptides can coexist with other classical neurotransmitters in large vesicles

#### **Release method:** Exocytosis

It depends on a small but continuous increase in concentration of  $\mbox{Ca}^{2+}$ 

- Metabolic pathway: Enzymatic degradation
- Effect modes: Autocrine

Paracrine

Endocrine Fric IN

Eric, J. N., Steven, E (2009)

## Alternative splicing and post-translational modifications cause neuropeptide diversity

![](_page_49_Figure_1.jpeg)

![](_page_49_Figure_2.jpeg)

Eric, J. N., Steven, E (2009)

## Most neuropeptide receptors belong to the G protein coupled receptor family

![](_page_50_Figure_1.jpeg)

G-protein coupled receptors that activate ion channels

## Most neuropeptide receptors belong to the G protein coupled receptor family

![](_page_51_Figure_1.jpeg)

G-protein coupled receptors that activate second messengers

## Neuropeptides have functional diversity

![](_page_52_Figure_1.jpeg)

![](_page_53_Picture_0.jpeg)

## NPF is an evolutionarily conserved brain-gut peptide

A. Amino acid sequences of members of the invertebrate NPF family.

Drosophila NPF Aplysia NPF Lymnaea NPF Helix NPF Moniezia NPF Artioposthia NPF SNSRPPRKNOVNTMADAYKFLQDLDTYYGDRARVRFa DNSEMLAPPPRPEEFTSAQQLRQYLAALNEYYSIMGRPRFa TEAMLTPPERPEEFKNPNELRKYLKALNEYYAIVGRPRFa STQMLSPPERPREFRHPNELRQYLKELNEYYAIMGRTRFa PDKDFIVNPSDLVLDNKAALRDYLRQINEYFAIIGRPRFa KVVHLRPRSSFSSEDEYQIYLRNVSKYIQLYGRPRFa

B. Sequence comparisons for *Drosophila* NPF relative to constant amino acids of members of the NPY / PYY / PP family.

Drosophila NPF NPY constant<sup>†</sup> PYY constant PP constant

![](_page_54_Figure_6.jpeg)

 $x_n Px Rx_n YL x_2 Lx_2 YY x_4 RPRF$ 

![](_page_54_Picture_8.jpeg)

![](_page_54_Figure_9.jpeg)

Mark, R. Brown (1999)

## Diverse aspects of behavior and physiology regulated by NPY in mammalian

Feeding
Energy homeostasis
Stimulation of food intake
Alcohol consumption
Circadian rhythms
Reproduction
Anxiety Seizure
Learning and memory

## Behaviors regulated by NPF in Drosophila

![](_page_56_Figure_1.jpeg)

## NPF signaling in feeding behavior

➢A pair of SOG neurons in the larva expressing NPF responds to gustatory exposure to sugar

►NPF expression correlates with developmental stage and is linked to active feeding behavior

>NPF signaling regulates motivation to feed

![](_page_57_Picture_4.jpeg)

![](_page_57_Figure_5.jpeg)

## NPF signaling in courtship and aggression behavior

![](_page_58_Figure_1.jpeg)

Lee, G.H (2006)

Dierick, H.A (2007)

Courtship Index (%)

50

## NPF signaling in post-mating behavior

![](_page_59_Figure_1.jpeg)

Ameku, T (2018)

NPF signaling in internal states

![](_page_60_Figure_1.jpeg)

NPF is the signal of the brain's reward systems

## NPF signaling in learning and memory

![](_page_61_Figure_1.jpeg)

Krashes, M. J (2009)

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# The differences and similarities between neurotransmitter, neurohormone and neuropeptide

	Neurotransmitter	Neurohormone	Neuropeptide
Chemical properties	Acetylcholine Amino acids Biogenic amines Purines	Polypeptides Steroids Amines	Polypeptides (3-50 amino acids)
Synthetic sites	Nerve terminals	Cell body	Cell body
Storage sites	Small clear-core vesicles Large dense-core vesicles		Large dense-core vesicles
Metabolism	Enzymatic degradation Reuptake	Liver Kidney	Enzymatic degradation
Release	Exocytosis	Exocytosis Diffusion	Exocytosis
Receptors	GPCR Ion tropic receptors	Nuclear receptors Trans-membrane receptors	GPCR
Secretion	Synaptic	Endocrine	Autocrine, Paracrine, Endocrine
Effect feature	Rapid	Longer-lasting Longer-distance	Longer-lasting

## Award-winning quiz

## What Defines a Neurotransmitter?

- 1. The substance must be present within the presynaptic neuron.
- 2. The substance must be released in response to presynaptic depolarization, and the release must be Ca2+-dependent.
- 3. Specific receptors for the substance must be present on the postsynaptic cell.

![](_page_67_Figure_4.jpeg)

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## Why is the function of neuropeptides diverse?

![](_page_68_Figure_1.jpeg)

## Which dilps definitely function as neurohormones

- DILP2
- DILP3
- DILP5

Thank you

To be continued...