A Possible Reward Prediction Error Circuit Exists in Brain: Around Prefrontal Cortex and Ventral Tegmental Area

Yongzong Yang

Abstract

This work aims to find a potential neuronal circuit from the Prefrontal cortex to the ventral tegmental area. In neurology, previous research focuses on how signal transfers from the ventral tegmental area to the Prefrontal cortex. Theoretically, the Prefrontal cortex is an effector and a processor. Therefore, a possible circuit, using the Prefrontal cortex as the departure, could be designed to find. This work is designed to employ some techniques, floxed genes, neuronal virus tracing, and an electrical detector in the brain to prove the desired circuit and give some prediction results. Those results will prove whether the neuronal circuit existed or not. If the electrical signals from the PFC region to VTA can be detected in termination, such a desired circuit is possible. This work may help to complete the learning mechanism, reward prediction error system, physiologically.

Keywords-Reward prediction error, Prefrontal cortex, ventral tegmental area, neuronal circuit

1. Introduction

The learning mechanism maintains the temptation for all the persons who want to address it. In the last century, some people raised that the brain may exist a perfect system called reward prediction error (RPE) system, which judged all possible outcomes and proposes a hypothetical expectation. For the discrepancy between expectation and result, RPE system has reflecting responses: Excitatory, null and inhibitory stimulation in dopamine (DA) neuron, which is pivotal for the RPE system [1]. For the aforementioned responses, they are corresponding that when reward more than prediction, reward nearly equal to the prediction and reward less than the prediction, respectively. These responses will be reserved in a special yet not clear way and produce effect to all latter predictions, involved the same thing. Although the memory mechanism and involved neural circuit are vague, some potential circuits that play an essential role in RPE system could be found since these PRE circuits are existing and when a species who employs RPE system and has study behavior, it will leave the PRE circuits. Hence, where these potential circuits probably are located and how to detect them become the problem to be solved.

Some previous researches propose some area in brain, which are possibly involved in RPE working. To be specific, several areas has influence in RPE system: prefrontal cortex, ventral tegmental area and dopamine neuron, they play the different role in brain and RPE system. The Prefrontal cortex (PFC) plays a marked role in our brain. Many scientists have claimed that the function of PFC has indispensable relation with a person's will and personality [2]. As for its connection with RPE, Ribas et.al mentioned that the medial Prefrontal cortex (mPFC) manages the signal from upstream and sends it in downstream neural circuit and finally reach the effector [3]. In a nutshell, PFC is the central area in the PRE system, being responsible for "superior and subordinate" signals. Meanwhile, another area which is as important as the PFC called ventral tegmental area (VTA) with no specific anatomical borders, working on RPE related mechanisms and orgasm or other stimulation transmission [4-6]. VTA seems receiving the signal from the PFC, and conduct the signal to the DA neurons, since it's located in termination along the PFC to DA, as the Figure 1 illustrates. Recently, more and more authors delineated the subsistent neuronal circuit between the VTA and PFC area, which showed the functional coupling for the RPE [7].

Besides PFC and VTA in the RPE system, GABA neuron also play a part in the system [8]. GABA, according to the Sigel and Steinmann, an inhibitory neurotransmitter, which declines the electrical signals from the upstream neuron and conduct the lower signal to the next neuron [9]. In the RPE system, when the prediction is higher than results, GABA will inhibit the electrical signal from the PFC and transfer it to the VTA. Therefore, how can illustrate the relation in PFC, VTA and GABA is important.

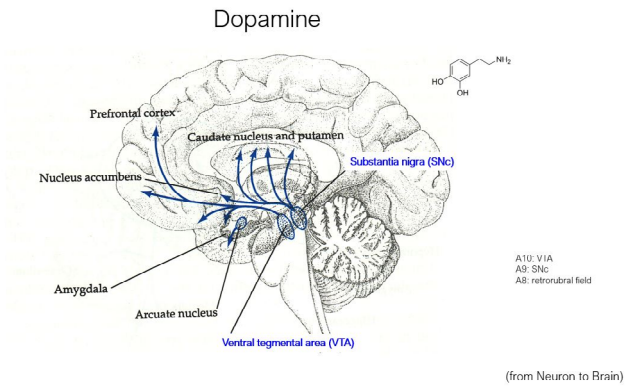

Figure 1. The structure involving DA neurons [10].

Though the major researches about the RPE focused on the circuit between the VTA and PFC area, most of them targeted the previous neuronal circuitry from VTA to the PFC. Few of them essayed to find the posterior neuronal circuitry from PFC back to the GABA neuron and finally to the downstream neurons in the VTA [5]. The PFC was a superior processing center in the RPE, and exert an exhibitory or inhibitory influence in dopamine neuron through multiple pathways [11]. Furthermore, whether the informational input from the VTA or the consequent results recording to the DA neuron, both revealed the possible RPE circuit around PFC and VTA neuron [12].

As for the behavioral paradigm, some previous groups conduct experiment in several species, such as pigeons and rhesus monkey [13,14]. The former, pigeons as the subject, experiment shows that when pigeons receive better reward than expectation, PFC region and VTA will have abnormal and higher excitement than normal state[13]. This result provides potential behavioral paradigm to find a possible circuit. Meanwhile, the latter, rhesus monkey as the subject, experiment implies that when unexpected events drive learning, PFC are unexpectedly and previously activated[14]. This result also provides evidence that PFC may locate in upstream neuron. These researches supply significant behavioral paradigm.

2. Methods and Materials

In this experiment, some techniques should be employed and experimental progress will be proposed. Since the GABA neuron located in rostral and medial range in VTA, this experiment expects find the circuit from PFC through GABA neuron and finally reaches VTA [8]. Since three parts are involving the circuit, this experiment should cover all parts to prove the circuit is existed.

Here give a briefly explanation to the whole process and below will minutely illuminate all the techniques employed: First, thirty healthy and mature mice will be the subject. Second, using retrograde virus neuronal tracing at the starter cell, GABA neuron to reach the PFC. If the virus attached with the floxed gene, it can help the silence gene in the PFC cells to express. One silence gene in mouse gene can express channelrhodopsin, which is the light detecting photoreceptor [15]. When light source irradiates the protein, if it is located in PFC neuron since virus make it be expressed, it will be stimulated and produce signal in the neuron and finally reach the VTA neurons. In final, if an electric detector apparatus placed in VTA can discover the signal, it will show that the desired circuit from PFC through GABA to the VTA is existed.

2.1 Neuronal virus tracing

Neurotropic virus, cannot replicate and grow individually, following the nature of general virus. Neuronal virus is generally divided into two kinds: high virulence with less transmissibility or low virulence with high transmissibility [16]. In those viruses, one of the viruses always utilized in neuronal biology, rabies virus. Recently research contends that inactivated rabies virus is a powerful and practical neuronal tracker, since it strictly obeys the particularly unidirectional (retrograde) transneuronal transfer [17]. Therefore, it can stepwise show upstream neurons on the starter cell, the first cell that rabies virus infecting. Meanwhile, according to Davis et.al, rabies virus works in synapses, from the postsynaptic to the presynaptic [18]. This provides the possibility that rabies virus can reach PFC from the GABA neuron.

The actual operation acquires more details. First the virus should only infect the GABA neurons. On the grounds of this, the GABA's promoter is needed to make rabies virus only express in it. For this, Hoshino et.al designs a GABAergic special promoter, mGAD65 promoter, which have specified and efficient nature [19]. Hence, genetically modified rabies virus can just express in the desired cell, GABA neurons.

What's more, another research proves that the protein in the virus shell will affect the tracing distance, deciding it producing the mono-neuron transfer, multi neuron transfer and the direction [20].

The virus tracing can spread retrogradely or anterogradely [21]. If the virus transfers retrogradely, its shell need attach PRV - pseudorabies virus protein, and such virus is PRV virus variant [20]. As for rabies virus, Ugolini states that it strictly obeys the retrogradely tracing [17]. Whereby this, the virus can transport from GABA neuron to the PFC circuit if the desired circuitry subsists, and the virus tracker should be RPV attached rabies virus tracker(See Figure 2).

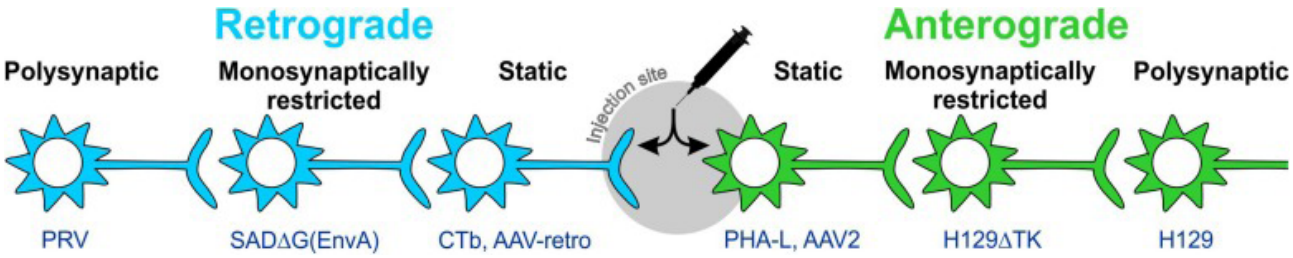

Figure 2: Directional virus tracing [18].

2.2 *Floxed gene*

The gene which expressing channelrhodopsin generally is a silent gene in the mouse [22]. This project can employ the floxed reporter gene to express the silent gene [23]. Hence, the light source can stimulate the circuit which the virus arrives at.

To be detailed, floxing is a process usually used by geneticists. Through this process, a target gene will have two loxP sites in two flanks. Once two loxP sites forming, scientist can modify the sequence between the two loxP sites spatially and temporally. By this process, the silent gene can be express since the promotor will be added before the gene with the correct direction.

In this project, the method to express the channelrhodopsin involved gene is using genetically modified mice. The viruses' gene should be modified into desired sequence. When they reach the PFC, they will invade the PFC neuron and amplify in the host. Once their gene connect with host, the promoter will be appended into the gene, and silent gene will be activated. Therefore, channelrhodopsin will appear in the PFC neuron.

Channelrhodopsin, a protein that sensitive to light. If light source irradiates it, it will produce the electrical signals in the neurons where it is attached [22]. Therefore, it can help to determine whether the circuit existed and the virus coming, since the consequence is the signal will be made in the upstream and conduct to the downstream. If the downstream signal can be detected, the whole circuit could be proved.

2.3 *Electrical current detection*

After light stimulation, the signal will conduct anterogradely and eventually reach the VTA neuron. The voltage detection apparatus need be placed in the VTA range to detect the voltage variation.

Here are some techniques in the science circle that can detect the variation happened in the brain, one of it is appropriate for the demand called Magnetic resonance (MRI), which can clearly reflect the current change in mice brain [24]. What's more, once the variation detected in VTA range, the desired circuit could be proved.

2.4 *Subject operation*

For the completeness, two control group can be set as the supplement. For the first one (Control set 1): Light should turn off and other situations sustain same. For the second one (Control set 2): Virus should not attach the reporter gene but with the particular protein and other conditions maintain.

3. Prediction Results

3.1 *Desired result*

Experiment set: The voltage detected in DA neuron should be lower than the normal stage, which testifies that the desired circuitry exists and has the capacity to inhibit the DA neuronal activity.

Control 1 set: The voltage maintains the normal stage, not obvious variation, which proves that the channelrhodopsin stimulate the circuit in PFC.

Control 2 set: The voltage maintains the normal stage, not obvious variation, which proves that the gene involved channelrhodopsin is silent gene.

Summary: The circuitry inhibits the activity of DA neuron, which reaches the DA neuron and from PFC through GABA neuron.

3.2 *Other results*

Results 1

Experiment set: The voltage detected in DA neuron should be higher than the normal stage, which testifies that the desired circuitry exists and has the capacity to excite the DA neuronal activity.

Control 1 set: The voltage maintains the normal stage, not obvious variation, which proves that the channelrhodopsin stimulate the circuit in PFC.

Control 2 set: The voltage maintains the normal stage, not obvious variation, which proves that the gene involved channelrhodopsin is silent gene.

Summary: The circuitry excites the activity of DA neuron, which reaches the DA neuron and from PFC through GABA neuron.

Result 2

Both experiment set and control sets: The voltage keeps nature value; distinct variation cannot be observed.

Summary: The circuitry does not exist.
Result 3
Both experiment set and control sets: The voltage is altered and the variation appears.
Summary: First, the virus itself may has influence in circuit. Subsequently, the circuit is existed.
Result 4
Experiment set and control 2 set: The voltage is changed and evident variation arises.
Control 1 set: The voltage sustains normal value with null phenomenon.
Summary: The gene related channelrhodopsin may express and is not silent gene in this situation.
Result 5
Experiment set and control 1 set: The voltage has noticeable change and variation occurs.
Control 2 set: The voltage maintains the normal value and no obvious variation arises.
Summary: The floxed reporter gene may have effect to stimulate the circuit, which exist in this result.

4. Conclusion

This experiment strictly considers probable situations and makes some predictions on the possible results. But at the same time, there are a few shortcomings in this experiment. First, contingency echoes this project, circuit may exist but with the frustrated results and cannot be testified. Second, the safety of mice is not well guaranteed. Nevertheless, this experiment sufficiently utilizes available technology, translating the existence of a circuit into observations of potential differences across several different brain regions, while minimizing damage to the mice.

Brain is miraculous in people perspective. There seems to be endless to the research of the brain. Meanwhile, the study of learning mechanisms also attracts countless people. At present, most of information about RPE are around DA neuron. The real mechanism and whether DA neuron is the core of the RPE need to be illustrated further.

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