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Review

Do dorsal raphe 5-HT neurons encode "beneficialness"?

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ABSTRACT

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) affects numerous behavioral and physiological processes. Drugs that alter 5-HT signaling treat several major psychiatric disorders and may lead to widespread abuse. The dorsal raphe nucleus (DRN) in the midbrain provides a majority of 5-HT for the forebrain. The importance of 5-HT signaling propels the search for a general theoretical framework under which the diverse functions of the DRN 5-HT neurons can be interpreted and additional therapeutic solutions may be developed. However, experimental data so far support several seeming irreconcilable theories, suggesting that 5-HT neurons mediate behavioral inhibition, aversive processing, or reward signaling. Here, we review recent progresses and propose that DRN 5-HT neurons encode "beneficialness" – how beneficial the current environmental context represents for an individual. Specifically, we speculate that the activity of these neurons reflects the possible net benefit of the current context as determined by $p \cdot R - C$, in which p indicates reward probability, R the reward value, and C the cost. Through the widespread projections of these neurons to the forebrain, the beneficialness signal may reconfigure neural circuits to bias perception, boost positive emotions, and switch behavioral choices. The "beneficialness" hypothesis can explain many conflicting observations, and at the same time raises new questions. We suggest additional experiments that will help elucidate the exact computational functions of the DRN 5-HT neurons.

1. Introduction

Ancient Greek philosophers since Aristotle promoted the life goal of "eudaimonia", which means possessing sufficient physical, mental, and social resources (Waterman, 1993). Similarly, the ancient Chinese philosopher Confucius once said: "Wealth and power are what men desire". Under the pressure of survival and reproduction, an individual animal constantly looks for food, water, mating opportunity, and social dominance. It may frequently ask the questions, such as "does this place have what I need", "have I just received something good", "should I stay here or explore other places", and "have I had enough for now". Answering these questions requires the critical information whether the current environment is associated with rewards with values higher than cost, or "beneficialness".

Is there a defined set of neurons in the brain that broadcast beneficialness signals? Based on recent physiological, neuropharmacological, and optogenetic studies, here we propose that the 5-HT neurons in the dorsal raphe nucleus (DRN) provide the beneficialness signal. These neurons project their axons to nearly all major brain areas and represent the major source of 5-HT in the forebrain (Vertes, 1991). Altering 5-HT levels or 5-HT signaling pathways affects numerous behaviors ranging from higher cognitive functions to basic physiological regulations, such as decision-making, learning and memory, perception, pain, emotion and mood, socio-reproductive behaviors, arousal, sleep, food intake, water and salt intake, body temperature, and respiration (Berger, Gray, & Roth, 2009). In humans, drugs targeting the 5-HT signaling system treat depression and may cause euphoria and hallucination (Aghajanian & Marek, 1999; Baylen & Rosenberg, 2006; Hirschfeld, 2000). In light of the widespread projections and the long list of affected behaviors, we would imagine that animals lacking 5-HT in the brain would have great difficulty in surviving. Paradoxically, laboratory tests often reveal rather mild behavioral deficits following 5-HT depletion.

The complexity and broadness of the behavioral effects suggest that it would be a daunting task to raise a general theory of 5-HT functions so that sometimes apparently conflicting observations could be harmoniously placed within a single umbrella. However,

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building a theoretical framework can be very valuable. This is best illustrated by the "reward prediction error" theory for dopamine neurons in the ventral tegmental area (VTA) of the midbrain (Schultz, Dayan, & Montague, 1997). Inspired by physiological recordings, this elegant theory explains many of the behavioral effects of dopamine, contributes to the understanding of reinforcement learning, and proposes testable hypotheses for further recordings and manipulations.

Several attractive theories have been proposed to explain the functions of the 5-HT neurons (Dayan & Huys, 2009; Hayes & Greenshaw, 2011; Kranz, Kasper, & Lanzenberger, 2010; Luo, Zhou, & Liu, 2015; Miyazaki, Miyazaki, & Doya, 2012a; Nakamura, 2013). The "behavioral inhibition" theory suggests that 5-HT is critical for controlling impulsive behavior, either to avoid punishment or to receive a delayed reward (Miyazaki, Miyazaki, & Doya, 2011a, 2011b; Soubrie et al., 1986). The "punishment" theory suggests that 5-HT neurons mediate behavioral responses to aversive stimuli and suppress reward processing by antagonizing the action of dopamine neurons (Daw, Kakade, & Dayan, 2002; Dayan & Huys, 2009; Deakin & Graeff, 1991; Soubrie, 1986). Finally, the "mood" theory suggests that 5-HT levels at slow time scales (minutes to hours) modulate mood (Daw et al., 2002; Savitz, Lucki, & Drevets, 2009).

Each of these theories receives support from certain neuropharmacological and neurophysiological studies and provide insights into the behavioral functions of DRN 5-HT neurons. However, as we will describe in detail, they also have limitations and thus far we have not reached a consensus on the exact functions of DRN 5-HT neurons. Ideally, a theory should derive from neuronal activity patterns during freely behaving states. It should also consider the widespread axonal projection of these neurons and the multifaceted effects on perception, cognition, and emotion and mood. Here we argue that the "beneficialness" concept agrees with the latest physiological recordings from animals and the major drug effects on humans, reconciles some apparent discrepancies across a broad spectrum of behavioral tests, and makes falsifiable predictions for further experimental tests.

2. The connectivity of DRN 5-HT neurons

The DRN is located in the ventral region of the periaqueductal gray matter along the midbrain midline. Its principle neurons synthesize 5-HT as the key neurotransmitter and are often called 5-HT neurons for simplicity. About 9000 5-HT neurons are present in the mouse DRN and consists of about half of the total neuron population in this nucleus (Ishimura et al., 1988). In humans this nucleus contains ~160,000 5-HT neurons (Baker et al., 1991). In rodents, approximately two thirds of 5-HT neurons co-express vesicular glutamate 3 (VGluT3) and release glutamate in a VGluT3-dependent manner (Hioki et al., 2010; Liu et al., 2014; Qi et al., 2014). Moreover, about half of DRN neurons are non-serotonergic and express markers for glutamate, dopamine (DA), GABA and/or certain peptide transmitters such as somatostatin and vasoactive intestinal peptide (Paspalas & Papadopoulos, 2001).

DRN 5-HT neurons receive strong inputs from a broad range of forebrain and limbic structures. Densest inputs arise from the brain areas that participate in reward processing, emotion control, and behavioral homeostasis, such as the frontal cortex, extended amygdala, amygdala, lateral habenula, midbrain dopamine areas (the VTA and substantia nigra compacta), and certain subregions of the hypothalamus (Dorocic et al., 2014; Ogawa, Cohen, Hwang, Uchida, & Watabe-Uchida, 2014; Weissbourd et al., 2014) (Fig. 1). DRN 5-HT neurons in turn project their axons extensively to the forebrain, midbrain, and hindbrain (Vertes, 1991; Vertes & Kocsis, 1994), including areas associated with reward processing

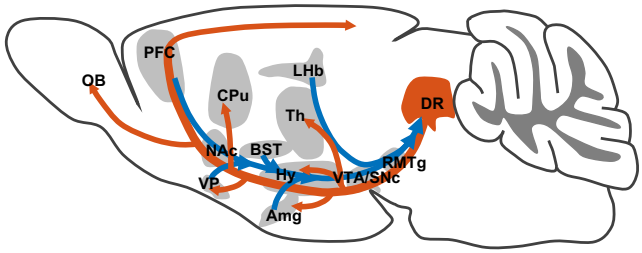

Fig. 1. The connectivity of dorsal raphe 5-HT neurons with the forebrain and midbrain. Efferents are shown in red and afferents in blue. Abbreviations: Amg, amygdala; BST, bed nucleus of the stria terminalis; CPu, caudate putamen; LHb, lateral habenula; Th, thalamus; Hy, hypothalamus; NAc, nucleus accumbens; OB, olfactory bulb; PFC, prefrontal cortex; RMTg, rostromedial tegmental nucleus; SNc, substantia nigra pars compacta; VTA, ventral tegmental area; VP, ventral pallidum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and emotion control (Fig. 1). They also project strongly to numerous sensory areas, including the sensory cortex, olfactory bulb, and thalamus. In contrast, they send relatively weak projections to the hippocampus and septal areas, which otherwise receive stronger inputs from 5-HT neurons in the median raphe nucleus (Azmitia & Segal, 1978).

In mammals, up to 15 receptors on the cell membrane mediates the effects of 5-HT (Barnes & Sharp, 1999; Filip & Bader, 2009; Hoyer, Hannon, & Martin, 2002) (Fig. 2). With the exception of the HTR3 receptors being ligand-gated ion channels, all the other 5-HT receptors belong to the large G protein-coupled receptor family. The HTR1 and HTR5 receptor families signal through $G_{i/o}$ and inhibit the activity of adenylyl cyclase, the enzyme that catalyzes the synthesis of cyclic adenosine monophosphate (cAMP). Both HTR1A and HTR1B receptors are richly expressed in 5-HT neurons, where they serve as inhibitory auto-receptors. The HTR2 receptors signal via G_q and activate phospholipase C, which catalyzes the production of diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3) and typically increases intracellular free Ca^{2+}. Finally, the HTR4, 6, and 7 receptors signal via $G_{\alpha s}$, activate adenylyl cyclase, and stimulate the increase of cAMP levels. The HTR1A, 1B, 2A, 2C, 3, 4, 5A, 6, and 7 receptors are expressed at moderate to high levels in the rodent brain and distributed in brain area-specific manner. Adding to the complexity, within a neuron different 5-HT receptors may be selectively distributed on somata, dendrites, and/or presynaptic terminals, thus differentially controlling postsynaptic spike firing and/or presynaptic neurotransmitter release. Finally, extracellular 5-HT is reabsorbed by serotonin

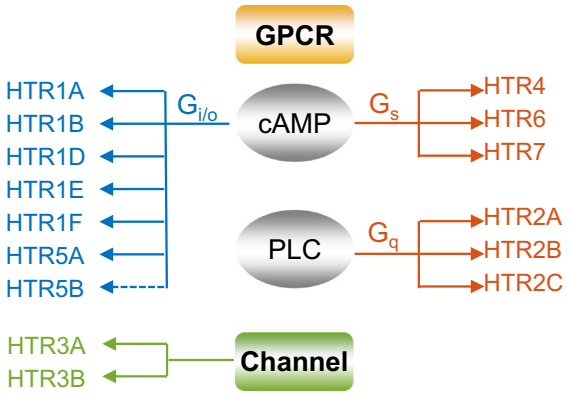

Fig. 2. 5-HT receptors in mammals. Abbreviations: 5-HTR, 5-HT receptor; GPCR, G protein-coupled receptor; cAMP, cyclic adenosine monophosphate; PLC, phospholipase C.