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Optogenetics in psychiatric diseases

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Abstract

Optogenetic tools have revolutionized the field of neuroscience, and brought the study of neural circuits to a higher level. Optogenetics has significantly improved our understanding not only of the neuronal connections and function of the healthy brain, but also of the neuronal changes that lead to psychiatric disorders. In this review, we summarize recent optogenetic studies that explored different brain circuits involved in natural behaviors, such as sleep and arousal, reward, fear, and social and aggressive behavior. In addition, we describe how alterations in these circuits may lead to psychiatric disorders such as addiction, anxiety, depression, or schizophrenia.

Introduction

Optogenetics allows functional interrogation of genetically identified neuronal circuits with unprecedented spatial and temporal precision. The application of optogenetic methods has allowed us a much deeper understanding of the basic circuits underlying complex behaviors, such as those hampered in psychiatric disorders. Here we summarize how optogenetics has advanced our knowledge on neuronal connectivity, and opened new possibilities in the study of psychiatric disorders.

Arousal and sleep

Arousal disturbances are tightly associated with many psychiatric disorders, such as depression, addiction and anxiety disorders [1]. Alterations between arousal states involve complex interactions between activity in populations of neurons that promote arousal and those that promote sleep [2]. The use of optogenetics lead to great progress in the study of two neuronal populations: the Hypocretin-expressing neurons and the noradrenergic locus coeruleus (LC) neurons. The Hypocretins (Hcrt1 and Hcrt2; also known as orexins) are a pair of neuroexcitatory peptides exclusively produced by a cluster of neurons in the lateral hypothalamus [3]. These neurons have a pivotal role in the stabilization and maintenance of wakefulness. In the first *in vivo* application of optogenetics in behaving animals, Adamantidis et al. [4] targeted ChR2 into Hcrt-expressing neurons, and showed that direct optical stimulation of these neurons during both NREM and REM sleep increased the probability of awakening (in the following 20-30 seconds). This induction was frequency-dependent; only a stimulating pattern of 5 to 30 Hz increased awakening probability, whereas a 1 Hz stimulation pattern did not. The arousal inducing effect of Hcrt-expressing neurons does not overcome homeostatic processes; Hcrt-mediated sleep-to-wake transitions were blocked by sleep pressure caused by sleep deprivation [5]. Optogenetic silencing of

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Hcrt neurons induced sleep during the light phase, but not during the dark phase [6]. These findings were further validated [7] using a newly developed pharmacogenetic technology (DREADD's; [8]) that allows the modulation of neural activity with temporal resolution of several hours.

The second central neuronal population in sleep-wake circuitry studied using optogenetics is the LC noradrenergic neurons. Optogenetic stimulation of these neurons caused immediate sleep-to-wake transition from both NREM and REM sleep [9]. As opposed to Hcrt neurons for which awakening occurred ~30 seconds following stimulation, stimulating LC neurons lead to an awakening event in less than 5 seconds from the initiation of the stimulation. Photostimulating LC neurons during wakefulness increased locomotor activity and total wake time, while photoinhibition decreased the duration of wake episodes but did not block sleep-to-wake transitions [9]. Interestingly, high-frequency stimulation of the LC neurons caused reversible behavioral arrests, resembling those seen in individuals suffering from neuropsychiatric disorders [9]. These results demonstrate that noradrenergic LC neurons activity is sufficient to promote wakefulness from sleep and general locomotor arousal but is not necessary for animals to wake from sleep. It has been recently shown that the effects of Hcrt neurons on sleep-to-wake transitions are dependent on noradrenergic LC neurons [10]. Photoinhibiting LC neurons during Hcrt stimulation blocked Hcrt-mediated sleep-to-wake transitions, whereas photostimulating LC neurons during Hcrt stimulation increased the probability of sleep-to-wake transitions [10]. Additional studies are needed to determine whether there are other neuronal populations necessary for the arousing effects of Hcrt neurons. There are somewhat contradicting evidence regarding histamine neurons [11], and future studies could clarify this issue.

Optogenetic methods offer vast new opportunities in sleep/wake research and deciphering the underlying neuronal network would allow manipulating this circuit in sleep-associated psychiatric disorders. For example, it is now possible to assess the relative importance of specific features of sleep to cognitive functions. Sleep continuity is disrupted in many psychiatric disorders, which are also frequently accompanied by memory deficits. Rolls et al. [12] used optogenetics to fragment sleep in mice without effecting its total duration or intensity. The authors photostimulated Hcrt-expressing neurons during the first hours of the inactive phase following learning of a novel object, and found that sleep fragmentation reduced learning and memory. Furthermore, they identified a minimum length of uninterrupted sleep required for proper memory consolidation. In addition to subcortical structures of the reticular activating system, thalamocortical systems are known to generate oscillations of cortical excitability associated with sleep/wake patterns. In particular, spindles, 8-12 Hz oscillations that accompany NREM sleep, have also been linked to memory consolidation processes. Several groups have now used optogenetics to manipulate PARV positive neurons in the reticular thalamus, which results in the generation of spindles [13]. Combining manipulations of sleep fragmentation with spindles will allow us to decipher the actual role of these features in cognitive function and disease.

Addiction

The prolonged exposure to drugs of abuse or alcohol induces persistent neuronal adaptations in the reward-seeking pathways leading in many occasions to addictive disorders. Optogenetics has importantly contributed to dissect the neuronal pathways related with reward seeking, and to identify the adaptations that take place in these circuits after the exposure to drugs of abuse [14-16]. Two highly interconnected brain regions play critical roles in mediating reward: the ventral tegmental area (VTA) and the nucleus accumbens (NAc). The VTA is a heterogeneous brain structure that contains different neuronal populations, which include dopaminergic, GABAergic and glutamatergic cells. Dopamine (DA) neurons in the VTA are the main effectors of reward. These DA neurons fire

constantly at a tonic rate, and when they fire phasically they induce reward. Voltammetry studies showed that optogenetic stimulation of VTA DA neurons mirror natural patterns of DA release in the striatum [17]. This allowed extensive optogenetic studies on the role of VTA DA neurons in reward. Phasic but not tonic optogenetic stimulation of DA neurons in the VTA induced conditioned place preference [18], and self-stimulation in both mice [19;20] and rats [21]. VTA DA neurons co-release glutamate together with DA, and optogenetic stimulation of these neurons elicits glutamatergic EPSCs in the NAc. Glutamate release cannot directly account for the typical reward-related responses of NAc neurons, but may modulate the long-term plasticity of cortical and limbic inputs that lead to addiction [22]. The VTA also contains GABAergic neurons that synapse directly onto DA neurons regulating their activity. It has been shown that activation of VTA GABAergic neurons *in vivo* suppresses the activity of neighboring DA neurons, and disrupts reward consummatory behavior. Cohen and colleagues [23] showed that DA neurons are sensitive to reward outcome whereas GABA neurons in the VTA are sensitive to the predicting cues. These studies suggest that the interplay between VTA DA and VTA GABA neurons can control the initiation and termination of reward-related behaviors, and encode prediction error discount.

Outputs from the lateral VTA, especially those activated by laterodorsal tegmentum neurons are integrated in the NAc, and mediate reward [24]. More than 90% of the neuronal population in the NAc are medium spiny neurons. As shown by optogenetic studies, they specifically target VTA GABAergic neurons, but not VTA DA neurons [25]. Medium spiny neurons are classified into two populations depending on the DA receptor they express (D1 or D2). Optogenetic studies provide evidence for an opposite role of these two pathways in reward-related behaviors. Optogenetic stimulation of D1 receptor-expressing (D1R) neurons induced persistent reinforcement, whereas stimulating D2 receptor-expressing (D2R) neurons induced transient punishment in operant and place conditioning tasks [26]. The NAc also contains cholinergic interneurons which constitute less than 1% of the local population. Nevertheless, the activation of cholinergic receptors in the NAc can strongly influence medium spiny neurons. Optogenetic studies demonstrated the importance of cholinergic interneurons in the NAc, by showing how the stimulation of cholinergic interneurons in the NAc inhibited the firing of medium spiny neurons [27], and induced DA release in this region [28].

In addition to the local innervation and the afferents from the VTA, the NAc receives glutamatergic inputs from the amygdala, the prefrontal cortex, the hippocampus and the thalamus [29]. Optogenetic studies explored the role of glutamatergic projections from the prefrontal cortex and the amygdala to the NAc in reward-seeking behavior. Interestingly, mice self-stimulated the basolateral amygdala, but not the prefrontal cortex glutamatergic afferents to the NAc. In addition, silencing basolateral amygdala afferents to the NAc reduced cue-reward associations [30]. Altogether, these data suggest that DA release from VTA neurons and glutamatergic projections from the basolateral amygdala activates the D1R neurons and facilitates reward seeking, while GABAergic external inputs from the VTA and local interneurons (cholinergic and D2R neurons) may inhibit the D1R neurons and turn down reward-seeking behavior.

The reward-seeking pathways experience neuronal adaptations after repeated exposure to drugs of abuse, often leading to addictive disorders. Several optogenetic studies show how the chronic administration of cocaine dysregulates the reward circuitry inducing responses that are not observed in naive subjects. Optogenetic activation of D1R neurons in the NAc had no effect on the locomotor activity of naïve mice, whereas it enhanced locomotor activity in mice repeatedly treated with cocaine [31]. Also, optogenetic stimulation of NAc D1R or D2R medium spiny neurons alone was unable to induce any type of place

conditioning. However, optogenetic stimulation of D1R neurons combined with a subthreshold dose of cocaine induced conditioned place preference. On the contrary, the effectiveness of cocaine inducing place preference at an active dose was reduced when D2R neurons were optogenetically activated [31]. Similarly, activation or inhibition of NAc cholinergic interneurons had no evident behavioral effects in naïve mice. However, while the optogenetic activation of NAc cholinergic interneurons could not induce place conditioning, the optogenetic inhibition of these neurons significantly reduced the efficiency of cocaine-induced conditioned place preference [32].

Glutamatergic inputs to the NAc, especially those coming from the prelimbic cortex, play a crucial role in the plasticity induced by repeated cocaine administration. Optogenetic studies show that stimulation of infralimbic cortex inputs to the NAc reverses long-term potentiation in NAc D1R neurons and behavioral sensitization induced by cocaine [33]. Also, inhibition of prelimbic cortex to NAc afferents blocks cocaine- and cue-induced reinstatement of cocaine-seeking [34].

Remarkably, inhibition of the reward circuit may also induce aversion. Optogenetic activation of GABA neurons in the VTA inhibited DA neurons and induces conditioned place aversion, and aversive stimuli increased the firing rate in these GABAergic neurons [35]. In addition, optogenetic activation of neurons in the lateral habenula, which mainly project to the medial VTA, inhibits those VTA neurons and induces conditioned place aversion [24]. These seemingly contradictory results (both activation and inhibition of VTA neurons inducing aversion) may be due to differences in activation patterns or recruitment of different neuronal ensembles by similar stimuli. At any rate, these results indicate that circuits that convey aversive and reward pathways are strongly related.

Fear, anxiety and depression

An exaggerated or prolonged exposure to conditions that induce fear or anxiety is the major cause of psychiatric disorders such as generalized anxiety disorder, post-traumatic stress disorder and/or depression. Using traditional techniques, a basic description of the fear circuit has been already delineated, however optogenetics now allow a deeper understanding of the functional anatomy of the neuronal populations involved in fear and anxiety.

Traumatic events generate robust and persistent memories. Both humans and animals learn that specific sensory cues or conditioned stimuli (CS) predict aversive events or unconditioned stimulus (US) by a form of associative learning called fear conditioning. The amygdala is a critical site for fear conditioning, and it is divided into different nuclei connected by highly organized circuits. The lateral amygdala (LA) integrates CS and US, and induces associative plasticity [36]. Supporting this, when optogenetic activation of pyramidal neurons in the LA is paired together with an auditory sensory cue it induces fear conditioning, in a similar way that an aversive stimuli does [37]. The LA projects directly and indirectly to the central nucleus of the amygdala (CE). While the LA integrates CS and US, the CE controls the elicitation of the conditioned response (CR). The CE is divided into two subnuclei; the lateral division of the CE (CEl) and the medial division of the CE (CEm), which contains a highly organized microcircuitry of GABAergic inhibitory neurons.

Optogenetic studies show that direct projections from the LA activate neurons in the CEI [38]. Also, the CEI transmits to the CEm, and the CEm transmits the information to other effector sites outside the amygdala. These studies also suggest that the CEI contains two populations that show opposite responses to the presentation of the CS after fear conditioning. CEI “on” neurons are activated with the presentation of the CS, whereas CEI “off” neurons are inactivated with the presentation of the CS. CEI “on” neurons modulate the activity of CEI “off” neurons, and CEI “off” neurons modulate the activity of CEI “on” and CEm neurons. Therefore, the presentation of the CS activates CEI “on” neurons, which inactivate CEI “off” neurons. Decreased activity of CEI “off” neurons disinhibits the CEm

and induces freezing [39;40]. Interestingly, the majority of CEI “off” neurons expresses oxytocin receptor [39], and a recent study showed that the optogenetic stimulation of oxytocinergic axons in the CE attenuates fear conditioning, and that the cell bodies of these oxytocinergic neurons are most likely located within the magnocellular subpopulation of the paraventricular nucleus of the hypothalamus (PVN) [41].

Brain regions that convey CS are also influenced directly by US. Studies using optogenetics show that the auditory cortex is activated by aversive US. Foot-shock activates cholinergic neurons in the basal forebrain. These cholinergic neurons activate GABAergic interneurons in layer 1 of the auditory cortex. Then, layer 1 interneurons inhibit parvalbumin expressing GABAergic interneurons in layer 2/3 of the auditory cortex, which at the same time inhibit pyramidal neurons of layer 2/3 [42]. Therefore, presentation of aversive stimuli induces a disinhibition in the auditory cortex. Disinhibition of pyramidal neurons by aversive stimuli might also occur in the visual cortex, indicating that aversive stimuli might influence the regions integrating CS for fear conditioning through pathways alternative to the amygdala [42].

Fear conditioning has a strong memory component, and the hippocampus plays an important role in the consolidation of fear-related memories. A very elegant study used novel optogenetic tools to express ChR2 in dentate gyrus neurons that were active during fear conditioning. Optogenetic reactivation of these neurons in a new context was sufficient to induce freezing. This indicates that the activation of a specific ensemble of cells involved in memory encoding is sufficient to retrieve fear memories [43]. In another study, Goshen and colleagues [44] showed that, contrary to the prevailing view, the hippocampus is required for the recall of fear memories at long times (~1 month) after conditioning, but that this requirement can only be revealed if optogenetic inhibition is carried out on a short time-scale (~5 min), presumably preventing the recruitment of compensating mechanisms.

Some of the circuits mentioned above not only control fear but also anxiety. Optogenetic studies have shown that glutamatergic projections from the basolateral amygdala (BLA) to the CE play an important role in anxiety. Optical activation of glutamatergic projections from the BLA to the CE decreases anxiety, whereas optical inhibition of these projections increases anxiety [38]. GABAergic projections from the CE to the bed nucleus of the stria terminalis (BNST) have been hypothesized to play a critical role in the control of anxiety. There is still no behavioral evidence that optogenetic activation of this pathway controls anxiety, however the optical activation of GABAergic neurons in the CE induced inhibitory currents in the BNST [45].

Depression is among the most disabling medical disorders and poses a serious public health concern [46]. Many patients suffer from treatment-resistant depression for which the only effective treatment to date is deep brain stimulation (DBS). Although DBS is used to treat different psychiatric and neurodegenerative diseases, it was until recently unknown what is the mechanism underlying its therapeutic benefits (i.e. whether they stem from the stimulation or the suppression of neuronal activity, and whether this is taking place in the local brain region or in other brain regions). Deisseroth and colleagues have started to elucidate the underlying mechanism by showing that the direct targets of DBS in the subthalamic nucleus (examined for Parkinson’s disease) are not local cell bodies but afferent axons probably arising from different regions [47]. Optogenetic tools were also used to study the role of the mPFC in depression [48]. In both humans suffering from treatment-resistant depression and in chronically socially-defeated mice there is a reduction in the expression of immediate early genes in the PFC [48]; indicating reduced neuronal activity in this region. Covington et al. [48] found that optogenetic stimulation of mPFC neurons

restored normal social interaction and sucrose preference in chronically socially-defeated mice.

Autism and schizophrenia

Social dysfunction is a common symptom in many psychiatric diseases [49]. Although human social behavior is much richer than that of typical rodent model organisms, a wide range of social behaviors can be studied using laboratory animals. Recently, the neuronal circuits underlying social behavior have started to be dissected using newly developed optogenetic tools. It has been hypothesized that behavioral deficits associated with psychiatric disorders, such as autism and schizophrenia, arise from elevation in the cellular balance of excitation and inhibition (E/I balance) within neuronal microcircuits [50;51]. This hypothesis was tested by optogenetically elevating the E/I balance in the medial-prefrontal cortex using a step-function opsin (SSFO) together with red shifted opsins (C1V1) [51]. Increased excitation in excitatory pyramidal neurons (but not inhibitory), lead to social and cognitive dysfunctioning which are similar to those seen in autism [51]. Cortical gamma oscillations are an indicator of enhanced information processing, which is highly affected in schizophrenic patients [52]. Recently, GABAergic inhibitory neurons that express parvalbumin as their calcium binding protein have been shown to have a causal role in the generation of gamma activity [53;54]. Additional studies are expected to advance our understanding on the contribution of local or large-scale cellular imbalances to information processing.

Aggression

Another aspect of social living for which there is an enormous negative impact in our society is aggression, but not much is known about its neurobiological bases. A neuronal population in the ventrolateral aspect of the ventromedial hypothalamus, which is a region previously shown to be activated during both aggression and mating, has been optogenetically targeted [55]. The authors revealed overlapping but distinct neuronal subpopulations involved in aggression and mating. Optogenetic activation of these neurons, but not electrical, induced aggression while pharmacogenetic silencing inhibited aggression. Interestingly, neurons that were activated during aggression were inhibited during mating [55].

Conclusions

One of the central hallmarks of psychiatric disorders is altered function in the communication between neuronal circuits. Using optogenetics it is now possible to study normal neuronal circuit function and dysfunction. Optogenetic studies have already contributed to a better understanding of the neural circuits affected in psychiatric disorders. New branches of optogenetics, which include cellular probing of signaling mechanisms and optical readout of neuronal activity are rapidly emerging and may set the stage for precise closed-circuit control and therapeutic intervention in human disease.

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Highlights

- Optogenetics allows manipulation of neuronal circuits using unprecedented specificity and temporal resolution;
- Optogenetics has identified networks in structures that play opposite roles in behavior such as reinforcement and aversion;
- Stimulation and inhibition of neurons using retrogradely transported viral vectors are uncovering new circuits regulating anxiety and depression;
- New branches of optogenetics, which include cellular probing of signaling mechanisms and optical readout of neuronal activity are rapidly emerging and may set the stage for precise closed-circuit control and therapeutic intervention in human disease.