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Review

Ventral pallidum roles in reward and motivation

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ABSTRACT

In recent years the ventral pallidum has become a focus of great research interest as a mechanism of reward and incentive motivation. As a major output for limbic signals, the ventral pallidum was once associated primarily with motor functions rather than regarded as a reward structure in its own right. However, ample evidence now suggests that ventral pallidum function is a major mechanism of reward in the brain. We review data indicating that (1) an intact ventral pallidum is necessary for normal reward and motivation, (2) stimulated activation of ventral pallidum is sufficient to cause reward and motivation enhancements, and (3) activation patterns in ventral pallidum neurons specifically encode reward and motivation signals via phasic bursts of excitation to incentive and hedonic stimuli. We conclude that the ventral pallidum may serve as an important 'limbic final common pathway' for mesocorticolimbic processing of many rewards.

Contents

1. Ventral pallidum function: moving beyond movement

The ventral pallidum was recognized as a distinct anatomical structure only a few decades ago. Heimer and Wilson first identified the ventral pallidum in 1975 as the primary output for the ventral striatum (nucleus accumbens), and suggested it served a role similar to globus pallidus in the striatal-pallidal circuitry for dorsal striatum (caudate-putamen) [1]. Previously the ventral pallidum often had been lumped with adjacent areas including the globus pallidus, substantia innominata, extended amygdala system, lateral preoptic area of hypothalamus (far rostral and lateral hypothalamus), or the polymorph layer of the olfactory tubercle. Today, however, its distinctive limbic-thalamocortical anatomical

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connectivity, and histochemical and neuronal makeup (e.g. high levels of substance P, enkephalins, and iron; heterogeneous cell types including cholinergic and GABAergic projection neurons; basal firing rates that are generally slower than dorsal pallidal but faster than striatal projection neurons), are recognized to distinguish ventral pallidum from other surrounding structures [1–16].

Notions of the ventral pallidum as a striatal output for movement, comparable to globus pallidus, contributed originally to a view that it functioned as a motor expression site [17,18]. For example, based on a series of behavioral studies, Mogenson et al. proposed that nucleus accumbens projections to the ventral pallidum translated limbic motivation signals into motor output [18,19]. This account attributed "limbic–motor integration" [19] to accumbens–pallidal systems, and specifically identified ventral pallidal projections to brainstem (e.g. pedunculopontine tegmentum) as a primary motor output for limbic motivation signals. However, transferring input from accumbens to brainstem motor-related targets is only one feature of ventral pallidum connectivity. The ventral pallidum is also a central convergent point for input from orbitofrontal, prefrontal and infralimbic cortex, the amygdala, lateral hypothalamus, ventral tegmental area, parabrachial nucleus, subthalamic nucleus, and other structures related to reward [20–35]. Conversely, the ventral pallidum projects back to nearly all of its input sources including the nucleus accumbens for reciprocal information exchange [8,13,36–41]. Further, ventral pallidum outputs re-enter corticolimbic loops via direct projections to medial prefrontal cortex, and dense projections to mediodorsal nucleus of thalamus, which relays in turn to prefrontal cortex [6,10,11,13,36,38,42,43]. Such limbic-related anatomical connectivity sets the stage for the ventral pallidum to mediate reward and motivation functions at many levels in the brain, beyond merely aiding translation to movement [35,40,44–54].

The most crucial evidence that ventral pallidum mediates reward, however, must come from actual functional demonstrations that ventral pallidum manipulations have consequences for reward. That is, do manipulations of ventral pallidum actually alter reward-related measures of neural activation and reward-directed behavior? Many such studies have now been conducted, which we review below. Together they provide strong evidence that the ventral pallidum is needed for normal reward, that it can add new reward value to stimuli, and that its neurons can encode reward and incentive motivation to gain external rewards.

2. The ventral pallidum is necessary for reward

2.1. Necessary for motivation to eat and hedonic impact

Perhaps the earliest experiments to implicate ventral pallidum in reward and motivation functions were a set of studies by Morgane that pushed the boundaries of food reward functions beyond the lateral hypothalamus to include the ventral pallidum and globus pallidus [55]. Morgane reported that electrolytic lesions to the globus pallidus (which now can be recognized to have damaged ventral pallidum), caused aphagia (failure to voluntarily eat) and adipsia (failure to drink) in rats, similar to lesions of the lateral hypothalamus [55–61], despite not damaging the lateral hypothalamus (the pallidal lesions being anterior, further lateral or dorsal to the hypothalamus). This early lesion study did not distinguish between globus pallidus and ventral pallidum, but rather damaged both, and used the name of globus pallidus for the entire damaged region. However, our own inspection of Morgane's lesions, as well as early lateral hypothalamic lesions, in published histological figures indicates the aphagia-inducing lesions damaged ventral pallidum as well as their intended target structure. These data, together with a later study that found that aphagia can be produced by lesions of the posterior ventral pallidum that do not invade globus pallidus or lateral hypothalamus [60], confirmed a role for the ventral pallidum as a key component of the neural system for eating and food 'wanting' [62].

The ventral pallidum may play an even more unique role in mediating reward beyond being necessary for motivated eating: it is the only structure known to us in which local lesions also eliminate normal 'liking' for sucrose, and replace it with 'disliking' [60]. 'Liking' is a second core component of reward, in addition to 'wanting,' and for many the most crucial. For natural food rewards, 'liking' has objective consequences in affective reactions patterns, such as orofacial reactivity patterns in response to tastes that are homologous across species [63–66].

Lesion studies of ventral pallidum and lateral hypothalamus have attempted to map the locus for a particular affective change in reward that often accompanied aphagia-producing lesions: the loss of acceptance or positive hedonic reactions to the taste of palatable food (such as tongue protrusions and lip licking), and replacement by active aversion reactions (such as gapes or headshakes). In the late 1970s, studies by Schallert and Whishaw [59] and Stellar et al. [61] found that active avoidance of food (e.g. withdrawal from a food- or chocolate-containing spoon) and aversion to intraorally infused food (e.g. ejection of the reward followed by aversion reactions like face washing) was produced by what was described as damage to the anterior portion of lateral hypothalamus [59,61]. That damage encroached on what is now known to be ventral pallidum. Active avoidance-aversion was not produced by damage to more posterior subregions in the lateral hypothalamus (which caused aphagia without active aversion) [59]. A later mapping study actually contrasted ventral pallidum, globus pallidus or lateral hypothalamic excitotoxin lesions, and found that active aversion to sucrose was caused only if a lesion damaged the ventral pallidum (specifically its posterior end, overlapping with part of the adjacent substantia innominata) [60] (Fig. 1).[1] Of note, the posterior and medial edge of ventral pallidum abuts the anterior and lateral edge of the lateral hypothalamus, and in fact, many classical electrolytic lesions of the lateral hypothalamus that produced aphagia with aversion also damaged the ventral pallidum as well as lateral hypothalamus [59,60]. This positioning may be important,

[1] The only other neural lesion known to cause active aversion to sweet tastes is the classic 'thalamic preparation', in which the entire telencephalon composed of all structures anterior to the thalamus is removed by suction ablation or similar surgery, leaving intact thalamus, hypothalamus, midbrain and brainstem [67,68]. Importantly, the 'thalamic preparation' may damage the ventral pallidum, which is part of the telencephalon, raising the possibility that ventral pallidum damage might similarly be responsible for the thalamic animal's aversion to sucrose. The importance to positive hedonic reactions of a ventral telencephalic structure such as ventral pallidum is emphasized by the consideration that basic hedonic reactions to taste are preserved in decerebrate animals transected above the superior colliculus but below most of the hypothalamus (with only the brainstem functioning) [68–70]. This presents a rather curious scenario: removing the ventral pallidum by itself or with the rest of the telencephalon, while leaving the diencephalic hypothalamus and thalamus as well as the brainstem, dramatically reduces hedonic reactions. But removing the ventral pallidum and telencephalon, *plus* the diencephalic hypothalamus and thalamus, fails to have much of an effect on hedonics. How can this be? For many behavioral functions, the brain contains a hierarchical organization such that brainstem signals are regulated by forebrain structures [71–74]. The taste pathway traverses through brainstem structures, such as nucleus of the solitary tract and parabrachial nucleus in rodents, then through the forebrain in bifurcating gustatory sensory paths (e.g. to gustatory thalamus then gustatory cortex) and limbic paths (e.g. to ventral pallidum) [75,76]. We have argued that basic affective and emotional reactions can be generated by the brainstem (e.g. in parabrachial nucleus: [77]), but in the normal intact brain these signals are under inhibitory control by forebrain hedonic structures like the ventral pallidum. This may be why we can observe relatively normal hedonics in decerebrated animals but impaired hedonics in animals with localized ventral pallidal lesions. See [74] and [54] for more detail.