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Functional aspects of the ventral pallidum

Review Article

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Summary. The ventral pallidum is part of the corticoaccumbo-thalamocortical loop of the basal ganglia. In the past the function of this structure was discussed as a pure relay station in the process of limbic-motor integration. Some recent studies, however, underline that on the level of the ventral pallidum motor behavior can be modulated. The stimulation and inhibition of the different transmitter systems that converge in the ventral pallidum (dopamine, glutamate, GABA, neuropeptides) have implications in repetitive-, disinhibited-, learning- and reinforced behavior. The present review summarizes available data of these parameter related to this behavior, i.e. locomotion, reward-related behavior, prepulse inhibition, memory and neurochemistry.

Keywords: Amino acids – Ventral pallidum – Corticoaccumbo-thalamocortical loop – Locomotion – Reward – Prepulse inhibition – Memory – Microdialysis

Introduction

The corticoaccumbo-thalamocortical loop of the basal ganglia is critically involved in the control of limbic-motor integration, a process of substantial impact for repetitive-, disinhibited- and reinforced behavior. Major interest was however focused on the functional implications of the nucleus accumbens (NAC) in the integrative process so far. The ventral pallidum (VP) as a lower basal ganglia structure was discussed as a pure relay station of information deriving from the NAC and reentering the cortex (Mogenson, 1987; Mogenson et al., 1993). However, similar to the NAC also the VP receives comprehensive innervation from limbic structures as well as from mesencephalic dopaminergic structures (Fuller et al., 1987; Klitenick et al., 1992). Glutamate and dopamine released by these afferents interact with

NMDA, AMPA, D1 and D2 receptors, respectively (Boyson et al., 1986; Albin et al., 1992; Page et al., 1995). Moreover, the VP receives GABAergic fibers from the NAC with substance P and enkephalin as cotransmitter (Groenewegen and Russchen, 1984). All the afferents terminate on GABAergic and cholinergic output neurons which innervate for example limbic structures, the mediodorsal thalamus, mesencephalic dopaminergic structures and motor regions in the brainstem (Groenewegen et al., 1993). Electrophysiological studies reveal that the neuronal activity of these efferents can be reduced by GABA-, μ and κ opioid receptor agonist- and dopamine D2 receptor agonist infusion and can be increased by glutamate-, substance P- and dopamine D1 receptor agonist infusion (Napier and Potter, 1989; Maslowski and Napier, 1991; Chrobak and Napier, 1993; Mitrovic and Napier, 1995).

Thus, due to the strategic position of the VP in the corticoaccumbo-thalamocortical loop and the extensive transmitter interaction integrative processing of behavioral information on the level of VP seems more than conceivable and some recent publications already confirmed this notion (see below). Furthermore, more previous data which have been the background of the contention that the VP is a relay station can indeed been discussed as studies supporting the important function of the VP as an integrative structure (Mogenson, 1987; Mogenson et al., 1993).

In the following paragraphs, recent findings on repetitive- (*i.e. locomotion*), reward-related- (*i.e. intracranial selfstimulation, conditioned place preference, self-administration and conditioned reward*), disinhibited- (*i.e. prepulse inhibition; food intake*), learning behavior and neurochemical findings from microdialysis studies are summarized.

Locomotor behavior

The corticoaccumbo-thalamocortical loop has been identified as associated with locomotor behavior a long time ago (see Mogenson, 1987). Ligands of the different transmitter systems of the VP modulate spontaneous as well as stimulated motor activity. However, there is no clear correlation of ligands increasing locomotion and those increasing neuronal activity of VP neurons or vice versa. It has been shown that intrapallidal infusion of the glutamate receptor agonists AMPA, kainate and NMDA (Shreve and Uretsky, 1989; Hooks and Kalivas, 1994; Johnson et al., 1996; Gong et al., 1997b; Kretschmer et al., 1999), of dopamine and dopaminergic ligands (Napier and Chrobak, 1992; Klitenick et al., 1992; Johnson et al., 1996; Gong et al., 1996; Fletcher et al., 1998), and of the μ opioid receptor agonists DAMGO and morphine and the δ opioid receptor agonist DPDPE (Austin and Kalivas, 1990; Hoffman et al., 1991; Anagnostakis et al., 1992) enhances spontaneous locomotion. Locomotion induced by AMPA- and DAMGO can be antagonized by simultaneous infusion of the GABAb receptor agonist baclofen into the VTA and that of DAMGO also by intrapallidal infusion of GABAa receptor agonist muscimol (Johnson et al., 1996; Austin and Kalivas, 1990). Thus,

increased activity of VTA and of GABAergic transmission in VP is involved in the motor response induced by these substances. However, DAMGO effects are not attenuated by 6-OHDA depletion of the NAC (Churchill et al., 1992), suggesting that VTA-NAC fibers are not intensively involved in locomotion induced by the μ receptor agonist. Since inhibition of VTA neurons attenuate DAMGO-induced locomotion (Johnson et al., 1996) activity of VTA-pallidal fibers are likely to be involved. This latter effect which is most probably dopamine-related because 30–60% of the VTA-pallidal fibers are tyrosine-hydroxylase positive (Klitenick et al., 1992) as well as the effects of dopaminergic agents are probably mediated through D1 receptors, since the D1 receptor agonist SKF 38393 but not the D2 receptor agonist quinpirole increases locomotor activity (Gong et al., 1998a).

Locomotion can be inhibited by intrapallidal administration of GABA (Jones and Mogenson, 1980), the D2 receptor agonist quinpirole (Gong et al., 1998a) or the κ opioid receptor agonist U50,488H (Hoffman et al., 1991). More specifically investigations of the GABA effects indicate that only novelty-induced locomotor activity but not activity of habituated animals is reduced after intrapallidal infusion of the GABAa receptor agonist muscimol (Austin and Kalivas, 1990; Hooks and Kalivas, 1995). Moreover, as it can be resumed from these data, blockade of the GABA receptor results in opposite responses; e.g. the GABAa receptor antagonists picrotoxin and bicuculline enhance motor activity, although the GABAb receptor antagonist phaclofen is ineffective (Mogenson and Nielsen, 1983; Austin and Kalivas, 1990).

Not only spontaneous locomotion can be modulated by ligands infused into the VP but also that induced by psychostimulants or by electrical stimulation. In this respect is has been shown that locomotor activity induced by systemic or intraaccumbal administration of dopaminergic agonists can be attenuated by the GABAa receptor agonist muscimol (Klitenick et al., 1992; Mele et al., 1998) or by the glutamate receptor antagonists DNQX and GAMS infused into the VP (Willins et al., 1992). Moreover, the GABAa receptor agonist muscimol is also able to reduce locomotor activity evoked by tetanic stimulation of the hippocampal CA1 region (Ma et al., 1996). Interestingly, motor responses elicited by the NMDA receptor antagonist MK-801 are unchanged after muscimol infusion into the VP (Mele et al., 1998).

Excitotoxic lesion of the VP results in transmitter-unspecific effects on locomotion. However, there are differences in the outcome depending upon the excitotoxin used; while ibotenic lesion increases spontaneous locomotion and reduces locomotion induced by the dopaminergic agonist amphetamine but not that of the NMDA receptor antagonist MK-801 (Mele et al., 1998), quinolinic acid lesion is without an effect on spontaneous as well as MK-801-evoked locomotion (Kretschmer, submitted).

Thus, blockade of VP output neurons seems to be most relevant for locomotor behavior induced by dopaminergic and endorphinergic ligands but less for those induced by glutamatergic ligands.

Reward-related behavior

Association of reinforcement or reward with dopaminergic function has a long tradition. Since more than 80% of dopaminergic VTA neurons terminate in the NAC most of the previous investigations regarding reward-related behavior were focused on the VTA-NAC axis. However, dopaminergic VTA neurons also innervate the VP as mentioned above. Moreover, apart the dopaminergic system also the glutamatergic system received considerable attention in reward functions (Bardo et al., 1998). Nevertheless, information about the implication of VP in reward-related behavior derived from a handful of studies using intracranial self-stimulation (ICSS), conditioned place preference (CPP), self-administration or conditioned reward (CR).

One method to examine whether a specified structure is involved in the reward process is to test if rats self-stimulate this structure. Indeed, it was shown that in the entire VP ICSS can be induced (Panagis et al., 1995) and that via this procedure c-fos expression increases in brain regions that are clearly related to reward processes; e.g. prefrontal cortex and ventral tegmental area (Panagis et al., 1997). Moreover, ICSS threshold in VP can be reduced by administration of cocaine, amphetamine or the D3 receptor agonist 7-OH-DPAT whereas the D1 and D2 receptor blocker haloperidol, SCH 23390, racloperide and sulpiride increase the ICSS threshold although they reduce motor performance at the same time (Panagis and Spyraki, 1996; McBride et al., 1999). These results show that rewarding properties of ICSS in VP can be increased by dopaminergic agents. Apart of the dopaminergic system also the opioid system is involved in this process. It has been shown that the μ opioid receptor agonist DAMGO is able to modulate ICSS-mediated reward but that there is however a regional heterogeneous function of the endorphinergic system in the VP; decreasing reward of DAMGO in the rostral VP and increasing reward in the caudal part (Johnson et al., 1993).

Similar to the ICSS studies also those testing the development of CPP or CR in VP reveal that intrapallidal infusion of the dopaminergic agents amplifies reinforcing properties related to this structure; i.e. amphetamine as well as cocaine induces CPP (Gong et al., 1996) and amphetamine also enhances responding of CR (Fletcher et al., 1998). Furthermore, the neurokinin substance P produced CPP when administered into the VP, a process that is sensitive to the neurokinin 1 receptor antagonist WIN 51,708 (Nikolaus et al., 1999). However, other transmitter systems apart of dopamine and substance P seem to be less involved in this process because neither AMPA nor the GABAa antagonist picrotoxin mediates CPP (Gong et al., 1997b) and picrotoxin does not increase responding of CR (Fletcher et al., 1998).

Lesion of the VP has also consequences on reward-related behavior. Excitotoxic lesions (ibotenate and NMDA) of the VP attenuate the development of CPP (McAlonan et al., 1993) and conditioned visual discrimination (Everitt et al., 1987), reduce cocaine and heroin self-administration (Hubner and Koob, 1990) and abolish CPP induced by systemic administration of amphetamine (Hiori and White, 1993). Moreover,

depletion of the dopaminergic system in the VP by 6-OHDA blocks CPP induced by cocaine (Gong et al., 1997a). However, VP excitotoxic lesion does not attenuate morphine-induced CPP and hypothalamic self-stimulation (Johnson and Stellar, 1994; Olmstead and Franklin, 1997).

Hence, dopamine is one essential transmitter in reward-related processes via VP whereas the function of other transmitters is still indefinite. Moreover, the VP modulates reinforcing values of drugs and behavior and seems most important in the acquisition or development of drug-related behavior. Some evidences seduce to speculate that VP functions need to be considered in learning processes that occur during the development of addiction.

Other behavioral parameter

Disinhibition of behavior such as prepulse inhibition (PPI) of the acoustic startle response and food intake in satiated animals has been shown also to depend upon the ventral corticoaccumbo-thalamocortical loop. However, only a few studies addressed the VP and these behavioral parameters. It has been shown that a PPI deficit is elicited by intrapallidal infusion of the GABAa antagonist pircotoxin but not by the GABAb antagonist saclofen (Swerdlow et al., 1990; Kodsi and Swerdlow, 1995). Moreover, a PPI deficit induced by dopamine infusion in or by lesion of the NAC can be antagonized by intrapallidal infusion of the GABAa agonist muscimol (Swerdlow et al., 1990; Kodsi and Swerdlow, 1994). VP lesion itself is without an effect on PPI but abolishes a PPI deficit induced by systemic apomorphine or intraaccumbal DA infusion (Kretschmer and Koch, 1998). However, VP lesion has no effect on a PPI deficit elicited by systemic treatment with the NMDA receptor antagonist MK-801 or intraaccumbal injection of the glycine receptor antagonist 7-chlorokynurenate (Kretschmer and Koch, 1998). Disinhibition of behavior can also be induced by intrapallidal infusion of the GABAa receptor antagonist bicuculline. This GABAergic blockade increases food intake in satiated rats (Stratford et al., 1999). These findings indicate that VP functioning is involved in disinhibiting of behavior which is sensitive to the dopaminergic- and GABAergic- but not to the glutamatergic system.

Additionally, VP seems also to be critically in memory processes. It has been shown that – although moderate – VP electrolytic lesion impairs the performance of object recognition and spatial memory (Ennaceur, 1998) and attention deficits can be observed after ibotenic or quisqualate lesion (Robbins et al., 1989). Further experiments are needed to describe the function of the VP in learning and memory more precisely.

Microdialysis study

Behavior and its dysfunctions can be related to neurochemical changes that can be found in specific nuclei. Microdialysis in freely-moving and behaving rats is therefore a perfect combination to investigate the neurochemical

background underlying behavior and behavioral dysfunctions. However, only a few studies examine transmitter status in the VP and motor behavior, simultaneously.

Microdialysis studies without behavioral correlation reveal that repeated systemic heroin injections produce a transient increase in opioid peptide levels (presumably enkephalins) in VP after the second injection an effect which is sensitive to naloxone pretreatment and that suggests that neurochemical adaptations in the VP may underlie opiate reward (Olive and Maidment, 1998). Infusion of the GABAa or the GABAb receptor agonists muscimol or baclofen via reversed microdialysis into the VP decreases GABA release in the VP, respectively (Bourdelais and Kalivas, 1992). These GABAergic fibers – most probably from the NAC – are furthermore able to modulate dopamine release from VTA-pallidal fibers. It has been shown that the GABAa and the GABAb receptor antagonists picrotoxin and phaclofen increased dopamine release in the VP, respectively and that picrotoxin augments dopamine release induced by the dopamine reuptake inhibitor GBR 12909 (Gong et al., 1998b). These latter data suggest a complex interaction of afferents terminating in the VP, if dopamine release is achieved via a direct interaction of dopaminergic and GABAergic fibers or via indirect effect of long- or short loop connection remains unclear so far.

Studies combining neurochemical and behavioral analysis indicate that the dopamine-releasing effect of the dopaminergic ligand cocaine correlates with its potency to induce CPP but not with its locomotion-inducing response (Gong et al., 1997a). In contrast, a correlation of locomotor responses and GABA release is found after systemic amphetamine or apomorphine treatment that enhances locomotion and reduces GABA release in the VP (Bourdelais and Kalivas, 1990, 1992; Mele et al., 1998). Thus, rewarding properties of dopaminergic ligands seem to depend upon dopamine release whereas locomotion-inducing effects of these drugs have a good correlation to GABAergic functions. In contrast, the non-competitive NMDA receptor antagonist MK-801 also stimulates dopamine release in the VP and increases locomotion when it is systemically administered, but it does not increase locomotion when it is intrapallidally infused although dopamine release is also enhanced in the VP (Kretschmer, submitted). Furthermore, MK-801 induced locomotion does also not correlate to GABA release in VP (Mele et al., 1998). Thus, neither dopaminergic nor GABAergic functions seem to be responsible for behavioral stimulation of the glutamate receptor antagonist MK-801. The glutamatergic system is however involved in behavioral activation in combination with neurochemical alterations via the VP as it has been recently shown in our lab; intrapallidal infusion of the glutamate receptor agonists NMDA and AMPA induced locomotor stimulation that is accompanied by dopamine and glutamate release in the VP (Kretschmer et al., 1999). Thus, dopamine has in contrast to glutamate once again a definite role in neurochemical processes conducted by the VP, that of glutamate is still not clearly definite.

Conclusion

VP functions have been shown to be involved in repetitive-, disinhibited-, learning- and reinforced-behavior as shown in locomotion, PPI and food intake under satiated condition, ICSS, CPP and CR, respectively. Thus the VP has similar properties as the NAC – the main input structure of the corticoaccumbo-thalamocortical loop- to influence limbic-motor integration. However, in contrast to the NAC, mainly functions of the dopaminergic system seem to depend critically upon the functional and transmitter-balanced integrity of the VP. This can be seen in the modulatory propertis of dopaminergic ligands in reward-related behavior, PPI and neurochemistry. Nevertheless, modulation of locomotion seems to be unrelated to a specific transmitter because it can be influenced by dopaminergic, glutamatergic, GABAergic and neuropeptidergic ligands. Thus, the function of the VP as a pure relay station needs to revised and the VP has to be considered as a critical structure in the processing of limbic-motor integration.

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