Alderson HL & Winn P (2005) The pedunculopontine and reinforcement. In JP Bolam, CA Ingham & PJ Magill (Eds.), *The Basal Ganglia VIII* (pp. 523-532). New York: Springer Science and Business Media. *In press*.

THE PEDUNCULOPONTINE AND REINFORCEMENT

Helen L. Alderson* and Philip Winn

1. INTRODUCTION

A rather older literature recognized clearly that the pedunculopontine tegmental nucleus (PPTg) was intimately wired into the basal ganglia. For example, the very first article in the very first issue of Brain Research concerned the projections of the lentiform nuclei and showed clearly projections from globus pallidus to PPTg (Nauta and Mehler, 1966). The renewed interest in this part of the brain was largely triggered by the introduction of choline acetyltransferase immunohistochemistry which enabled visualization, description and classification of cholinergic neurons, including those in the mesopontine tegmentum (Mesulam et al., 1983). Most recently, it has again been argued that the PPTg is a member of the basal ganglia family of structures and that understanding of its structure and function can only proceed effectively if we understand its position within this (Mena-Segovia et al., 2004). Functionally, it has been recognized for some time that the PPTg is involved with much more than simply the control of locomotion and sleep, as an older literature suggested. Many studies over the last decade have shown that the PPTg has something to do with reward and reinforcement. The purpose of this brief review is to describe the structure of the PPTg as it relates to the basal ganglia and to examine critically its role in reward and reinforcement.

2. ANATOMY OF THE PPTg

We present here a brief synopsis of what is known of the composition and connections of the PPTg. There are a number of recent reviews describing both the connections and functions of the PPTg (for example, Inglis and Winn, 1995; Pahapill and Lozano, 2000; Mena-Segovia et al., 2004) to which readers are referred for more details. It is also worth observing that the PPTg, like the basal ganglia (Marin et al., 1998), has

* Helen L Alderson, and Philip Winn, School of Psychology, University of St Andrews, St Mary's Quad, South Street, St Andrews, Fife, KY16 9JP, United Kingdom. Email for correspondence: hla@st-and.ac.uk

been very well conserved through evolution. There are many descriptions of its composition and connections in a variety of species (from teleost fish [Brantley and Bass, 1988] to humans [Mesulam et al., 1989]) that indicate its highly conserved nature.

2.1. Composition

The neurons of the PPTg are discriminable morphologically, neurochemically and electrophysiologically. The most obvious population of neurons in PPTg is the Ch5 cholinergic neurons that aggregate at the lateral tip of the superior cerebellar peduncle, though there are many non-cholinergic neurons medially adjacent to and interdigitated with them. Early descriptions of the region suggested that cholinergic and non-cholinergic neurons were separated and that the term "PPTg" should be reserved for the cholinergic neurons and "midbrain extrapyramidal area" used to describe the adjacent non-cholinergic neurons. This separation however is not as sharp as was supposed: there are clearly non-cholinergic neurons interdigitated amongst the cholinergic neurons.

PPTg cholinergic neurons contain other neurotransmitters and neuromodulators as well as ACh. Virtually all contain nitric oxide synthase (NOS) for production of the neurotransmitter NO (Vincent and Kimura, 1992) and subsets of the Ch5 group contain amino acid neurotransmitters (glutamate and GABA) or neuropeptides – substance P for example (Vincent et al., 1986; Bevan and Bolam., 1995; Charara et al., 1996). As yet, no systematic pattern of neurotransmitter co-existence has been described. The non-cholinergic neurons appear, for the most part, to contain GABA (Ford et al., 1995). Both cholinergic and non-cholinergic neurons appear in small (long axis <20 μm), medium (20-35 μm), and large (>35 μm) types (Takakusaki et al., 1997) and both typically have six primary dendrites. Cholinergic neurons are known to have extensive dendritic fields that often extend outwith the PPTg, and their axons (certainly of the cholinergic neurons) show extensive branching, in some cases with ascending and descending limbs (Semba et al., 1990). Electrophysiologically, populations of neurons differing in terms of ionic mechanism and burst firing properties have been described. For example, using *in vitro* slice preparations, Kitai and his colleagues (Takakusaki et al., 1997) describe two populations of neurons: less common non-cholinergic neurons with low-threshold calcium spikes and a more common type, predominantly but not exclusively cholinergic showing an A-current. Perhaps most interestingly though, when recorded *in vivo*, PPTg neurons show very short response latencies to sensory stimuli (Dormont et al., 1998).

2.2. Connections

There are extensive ipsilateral connections, with good evidence for at least some of the projections traveling to the contralateral hemisphere (Usunoff et al., 1999). The many connections are best described in groups. (i) There are descending connections to the spinal cord (Skinner et al., 1990), the pontine and medullary reticular formations (Jones, 1990; Semba et al., 1990) and the motor trigeminal (Fay and Norgren, 1997). There are also ascending connections to the PPTg from the deep nuclei of the cerebellum that are most likely branches of axons ascending to the thalamus (Hazrati and Parent, 1992). (ii) The Ch5 neurons of PPTg can be considered as archetypal members of the ascending reticular activating system (ARAS) – small numbers of cells giving rise to branched axons spreading over a wide area and having neuromodulatory functions – and, as expected, they are interconnected with other ARAS elements. There are both

noradrenergic and serotonergic inputs (Williams and Reiner, 1993; Honda and Semba, 1994), as well as connections with the contralateral PPTg (Leonard and Llinas, 1990). (iii) There are extensive connections with many nuclei of the thalamus – indeed, en masse, the cholinergic neurons of the mesopontine tegmentum innervate the entire thalamus. Projections from the PPTg have impact on both thalamocortical and thalamostriatal output (Erro et al., 1999). In more functional terms, unilateral stimulation of the posterior PPTg increases *c-fos* activation significantly in the centrolateral and ventrolateral nuclei ipsilaterally, and thalamic reticular nucleus bilaterally (Ainge et al., 2004). Other nuclei, such as the parafascicular have innervation (Kobayashi and Nakamura, 2003) and why these do not show increased Fos expression after posterior PPTg stimulation is unclear. One possible explanation is that different parts of the PPTg make differential innervations of the thalamus. (iv) As well as being able to effect cortical activity through the thalamus, PPTg has impact on sites of non-specific cortical input, including lateral hypothalamus and the basal forebrain. (v) There are extensive connections with corticostriatal and related systems (Figure 1). As well as innervating the thalamus, the PPTg makes a strong innervation of midbrain dopamine (DA) neurons: ACh has excitatory effects on both substantia nigra pars compacta (SNc) and ventral

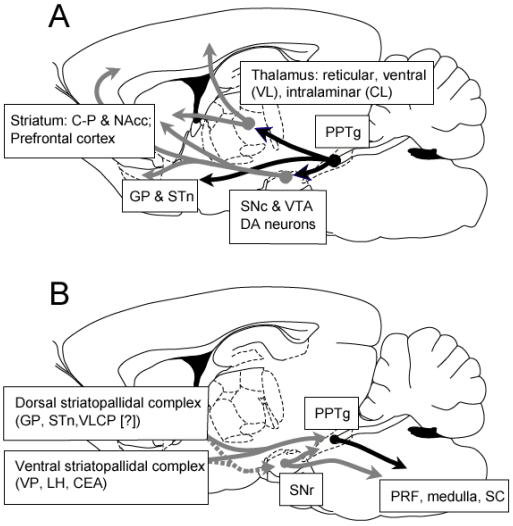

Figure 1: rat brain sections (Paxinos and Watson, 1997) showing (A) ascending and (B) descending PPTg – corticostriatal connections; black arrows show PPTg. *Abbreviations*: C-P caudate putamen; CEA central extended amygdala; CL centrolateral thalamus; GP globus pallidus; LH lateral hypothalamus; NAcc nucleus accumbens; PPTg pedunculopontine tegmental nucleus; PRF pontine reticular formation; SC spinal cord; STn subthalamic nucleus; SNc substantia nigra, compacta; SNr substantia nigra, reticulata; VP ventral pallidum; VLCP ventrolateral caudate-putamen; VL ventrolateral thalamus.

tegmental area (VTA) DA neurons (Bolam et al., 1991; Blaha and Winn, 1993; Blaha et al., 1996). The ability to drive DA neurons gives PPTg indirect control over the structures to which these neurons project, including of course the striatum and prefrontal cortex. In addition to these, there are also direct ascending connections with the subthalamic nucleus (Bevan and Bolam, 1995) and the globus pallidus (Mesulam et al., 1989). The PPTg also receives output from corticostriatal and related systems: the

substantia nigra pars reticulata (SNr), subthalamic nucleus and globus pallidus all project to the PPTg (Moriizumi and Hattori, 1992; Saitoh et al., 2003; Parent and Parent, 2004), as does the ventral pallidum and a significant tranche of the central extended amygdala (Zahm et al., 2001). There are also afferent and efferent connections with superior colliculus (Beninato and Spencer, 1986; Redgrave et al., 1987).

2.3. Functional Implications of PPTg Anatomy

This brief review gives evidence of the fact that the PPTg has a complex internal organization and an extensive set of afferent and efferent connections. The broad pattern of these can be conceptualized as follows: it receives polymodal sensory data that has as yet received little processing – from superior colliculus for example. The PPTg has output to thalamus and corticostriatal systems, as well as sites of nonspecific cortical input. It also receives output from corticostriatal systems and can be considered as an important basal ganglia output station. In addition, PPTg has descending output to sites in brainstem and spinal cord. This suggests that the PPTg is a route for sensory input to thalamus and basal ganglia and, in turn, mediates their output. It seems reasonable, therefore, to consider the functions of the PPTg in terms of the processing that is engaged by corticostriatal and thalamic systems. One of the principal functions of these systems is the analysis of incoming data and the formulation of appropriate behavioral responses. Key to this is learning about the relationships between stimuli and behavior.

3. REWARD AND REINFORCEMENT

The terms "reward" and "reinforcement" are commonly used in behavioural neuroscience, often interchangeably. However, their meanings are very different and it is important to define them. Reward is defined as the appetitive nature of a stimulus – that is, its incentive value, how valuable that stimulus is to the animal. The reward value of a stimulus – food, for example – is not constant, but changes according to the state of the animal. Food has a lower reward value to a sated animal than it does to a hungry one. Reinforcement is defined as the ability of a stimulus to support a learned behaviour. For example, food can be said to be functioning as a reinforcer when it is given following a lever-press, and the animal subsequently increases the rate of lever-pressing in order to receive more food. There is, of course, a relationship between reward and reinforcement: a stimulus that has rewarding properties can support reinforcement learning.

4. APPROACHES TO REWARD, REINFORCEMENT AND THE PPTg

The PPTg has long been associated with reward-related behaviours and a wide variety of methods have been used to investigate them in rats bearing PPTg lesions. These have ranged from simple measures of food and water intake in the home cage, to more complex assessments of the accuracy of reward perception using operant methods. Studies have examined natural rewards – predominantly food – and drug rewards. Interest in the involvement of the PPTg in mediating the rewarding effects of drugs of abuse in particular has been growing in recent times.

The most straightforward reward-related behaviour is the consumption of lab chow and water in the home cage, which is not affected by bilateral excitotoxic lesions of the PPTg (Allen and Winn, 1995). However, PPTg lesioned rats do show altered behavioural responses when given the opportunity to consume a sucrose solution. At low concentration there is no difference between PPTg lesioned rats and controls in the volume of sucrose solution drunk, but at concentrations of 12% and above, PPTg lesioned rats consume significantly more sucrose solution than do controls (Olmstead et al., 1999; Alderson et al., 2001; Keating et al., 2002). There are a number of possible explanations for this altered consumption of high-concentration sucrose solutions. Firstly, that a PPTg lesion somehow results in an alteration in the ability to regulate calorie intake. However, it has been found that PPTg lesioned rats reduce their lab chow consumption when offered high-concentration sucrose solutions so that their calorie intake is the same as when the only food source offered is lab chow (Keating et al., 2002). An alternative explanation for the over-consumption of high-concentration sucrose by PPTg lesioned rats is that they perceive it to be more rewarding than do normal rats. The perception of the reward value of sucrose has been measured using conditioned place preference (CPP) and negative contrast tests, and found to be unchanged by PPTg lesions (Olmstead et al., 1999; Alderson et al., 2001; Keating et al., 2002). It seems most likely that the over-consumption of sucrose by PPTg lesioned rats is due to a lack of behavioral control – a dysregulation of inhibition or switching for example – rather than an alteration in their perception of its reward value. In the context of natural rewards, it must be noted that CPP for food reward has been examined in rats bearing excitotoxic lesions of the PPTg, and it has been suggested that the deprivation state of the rat is an important factor controlling responding. PPTg lesioned rats were impaired in the acquisition of CPP for lab chow when food deprived, but not when they were non-deprived (Bechara and van der Kooy 1992a). However, in other studies deprivation state has not been a critical factor in determining the performance of PPTg lesioned rats (Keating et al., 2002).

Reward perception can also be measured by use of a progressive ratio (PR) schedule of operant responding. This requires the rat to perform an increasing number of lever-presses in an operant chamber in order to gain each successive reward. For example, under a PR5 schedule, the first reward would be delivered after 5 lever-presses, the second after 10, the third after 15, and so on. The point in the schedule at which an animal stops responding is known as the breaking point, and this is taken to reflect the perceived value of the reward to the animal: how hard it is prepared to work for the reward offered. PPTg lesioned rats show a reduced breaking point under a PR schedule of food reward, compared with controls, which might be interpreted as reflecting a reduction in the perceived reward value of the food. However, this reduced breaking point is actually a result of increased responding on the control, non-reinforced, lever and does not appear to indicate changes in reward perception (Alderson et al., 2002). Although responses to natural rewards are changed by PPTg lesions, this does not seem to be as a result of altered reward perception. Therefore, the PPTg does not appear to be involved in mediating the judgment of the rewarding impact of a stimulus such as food.

The rewarding properties of drugs of abuse have also been suggested to be functionally dependent on the PPTg. Several studies have been carried out examining CPP to drugs of abuse in PPTg lesioned rats, with mixed results. PPTg lesions have been found to impair the acquisition of CPP to amphetamine (Bechara and van der Kooy 1989; Olmstead and Franklin, 1994) but not cocaine (Parker and van der Kooy, 1995), a

result that is somewhat surprising given the similarities between the mechanism of action drugs. A number of studies have also found that CPP to morphine is impaired by lesions of the PPTg (Bechara and van der Kooy 1989; 1992b; Olmstead and Franklin 1994). However, in rats that have been made dependent on morphine, PPTg lesions are without effect on CPP to it (Bechara et al., 1992). One possible interpretation of these impairments in CPP following PPTg lesions is that the lesions block the rewarding effect of drugs of abuse, at least under some conditions. However, evidence from studies of intravenous self-administration (IVSA) of drugs of abuse, a more direct measure of drug reward, suggests that this is not the case.

The self-administration of several drugs of abuse has been examined following excitotoxic lesions of the PPTg. IVSA of heroin is impaired by PPTg lesions made before operant training occurs, but not by lesions made afterwards (Olmstead et al., 1998). Similarly, self-administration of *d*-amphetamine under a fixed-ratio schedule by rats bearing PPTg lesions was impaired when no pre-lesion training has been given, but not when an operant response had been acquired prior to lesion surgery (Alderson et al., 2004a). Both these studies suggest that the role of the PPTg is not to mediate the rewarding effect of the self-administered drug, but that the impairment is in the ability to acquire an operant response – that is, impaired reinforcement processes. The role of the PPTg in nicotine self-administration appears to be more complex. Corrigall and his colleagues (1994) reported that lesions restricted to the dorsal PPTg did not affect nicotine IVSA in rats trained prior to lesion surgery. A recent study from our laboratory (Alderson et al., 2004b) compared the effects of lesions of the posterior PPTg (pPPTg; pars compacta) and anterior PPTg (aPPTg; pars dissipata) on nicotine IVSA in rats given operant training prior to being lesioned. There was no effect of aPPTg lesions on nicotine IVSA, while rats bearing pPPTg lesions showed an increase in the number of infusions taken. This increase did not appear to be a result of an alteration in the rewarding impact of nicotine, because these rats showed a normal dose-response to nicotine, albeit responding at a higher level than controls, for all doses and saline.

Manipulation of the PPTg by local drug microinjections have produced mixed results. The μ-opioid receptor agonist DAMGO reduced both cocaine and nicotine IVSA, as did the muscarinic agonist carbachol (Corrigall et al., 1999; 2002) and the GABA agonists muscimol and baclofen (Corrigall et al., 2001). Cocaine IVSA was increased by intra-PPTg microinjection of the nicotinic receptor agonist DHβE (Corrigall et al., 1999). These data are difficult to interpret, beyond suggesting a role for the PPTg in drug self-administration and a complex local synaptology.

4.1. Theories I: Two-Motivational Systems Hypothesis

Derek van der Kooy and his colleagues developed the Two-Separate-Motivational Systems hypothesis of opiate reward, the only theory explicitly suggesting that the rewarding effect of opiates is mediated, under very specific conditions, by the PPTg. The central tenet (Bechara et al., 1998) is that opiate reward is mediated by the PPTg when users are in a drug-naïve state – not dependent on the drug – but by the DA system when in an opiate-dependent state. The authors also suggest that it is possible to use these theories to explain their finding that PPTg lesions impair CPP for food in sated rats, but not in those that are food-deprived. The theory suggests that these two systems operate independently: one takes over from the other once food deprivation or drug dependence (and hence withdrawal in the absence of drug) occurs. This theory is not supported by

experiments from other laboratories, including our own, regarding both the role of the PPTg in reward-related behaviour, and interactions between the PPTg and DA systems. Neurochemical and electrophysiological data support the notion of significant interaction between the PPTg and DA systems. As described above, PPTg innervates DA neurons in the VTA and SNc (Oakman et al., 1995); lesions of the PPTg alter striatal DA function (Blaha and Winn 1993); and PPTg stimulation elicits firing of midbrain DA neurons, leading to increased striatal DA efflux (Floresco et al., 2003; Forster and Blaha 2003). It is important to note here, first, that the relationship is not an opponent one, as the two motivational systems hypothesis implies, but co-operative; and second, that the hypothesis that DA systems are involved in motivation only in particular deprivation / dependent states is not supported (see Berridge and Robinson, 1998).

Behavioral studies, as discussed above, have found that CPP to sucrose was not impaired in PPTg lesioned rats, regardless of deprivation state (Keating et al., 2002), while operant responding for food reward was altered by PPTg lesions, but not in a manner suggestive of alterations in its rewarding effects (Alderson et al., 2002). Additionally, although acquisition of amphetamine was impaired by PPTg lesions, this was ameliorated by a pre-session priming dose of amphetamine, which presumably increased striatal DA levels. This is consistent with there being a close functional relationship between DA systems and the PPTg (Alderson et al., 2004a). Indeed, it may be possible to explain the findings of van der Kooy and his colleagues in terms of changed DA responsiveness rather than deprivation state. The available evidence certainly argues for a close co-operative relationship between the PPTg and midbrain DA system in mediating reward-related behaviour.

4.2. Theories II: Learning About Reward

There is a wealth of evidence from other studies suggesting that the PPTg is critically involved in reinforcement learning rather than in mediating the rewarding effects of stimuli. Midbrain DA neurons are critically involved in reinforcement learning (see Schultz, 2002 for review) and they are dysfunctional following excitotoxic lesions of the PPTg (Blaha and Winn, 1993). We suggest that the functional integrity of the PPTg is necessary for reinforcement learning because of its involvement in modulating midbrain DA activity. A number of studies have found impairments in relatively complex learning following excitotoxic lesions of the PPTg. The acquisition of responding for conditioned reinforcement is impaired (Inglis et al., 1994; Inglis et al., 2000) as are discriminated approaches in an autoshaping paradigm (Inglis et al., 2000). The reduction in breaking point under a progressive schedule of food reward following PPTg lesions can also be interpreted as a learning impairment (Alderson et al., 2002): the breaking point reduction was accompanied by increased responding on the non-reinforced control lever, suggesting a problem in the associative processes linking lever and reward. Evidence for the involvement of the PPTg in reward-related learning also comes from examination of amphetamine self-administration in PPTg lesioned rats (Alderson et al., 2004a). In conditions in which operant behavior had been acquired prior to PPTg lesion surgery, there was no effect of such lesions on amphetamine self-administration. In contrast, if lesions were made prior to training, acquisition of amphetamine self-administration was impaired, a problem ameliorated by non-contingent priming with amphetamine

7. CONCLUSIONS

Consistent with the role that the PPTg has in the regulation of midbrain DA activity, we conclude that the functional integrity of the PPTg is necessary for reward-related learning but not for the maintenance of previously acquired rewarded behavior. This conclusion is consistent with the connectivity of the PPTg: it makes fast responses to sensory data, relaying this to the thalamus and, via midbrain DA neurons, to corticostriatal systems. It is also an important basal ganglia output station, with descending connections to pontomedullary and spinal cord sites. The structure of PPTg is strongly reminiscent of the substantia nigra: we believe that its function might be too.

8. ACKNOWLEDGMENTS

Our work is supported by generous grants from the Wellcome Trust and the BBSRC.

REFERENCES

Ainge, J.A., Jenkins, T.A. and Winn, P., 2004, Induction of *c-fos* in specific thalamic nuclei following stimulation of the pedunculopontine tegmental nucleus, *Eur. J. Neurosci.* **20**:1827.

Alderson, H.L., Jenkins, T.A., Kozak, R., Latimer, M.P. and Winn, P, 2001, The effects of excitotoxic lesions of the pedunculopontine tegmental nucleus on conditioned place preference to 4%, 12% and 20% sucrose solutions, *Brain Res. Bull.* **56**: 599.

Alderson, H.L., Brown, V.J., Latimer, M.P., Brasted, P.J., Robertson, A.H. and Winn, P., 2002, The effect of excitotoxic lesions of the pedunculopontine tegmental nucleus on performance of a progressive ratio schedule of reinforcement, *Neurosci.* **112**:417.

Alderson, H.L., Latimer, M.P., Blaha, C.D., Phillips, A.G. and Winn, P., 2004a, An examination of d-amphetamine self-administration in pedunculopontine tegmental nucleus-lesioned rats, *Neurosci.* **125**:349.

Alderson, H.L., Latimer, M.P. and Winn, P., 2004b, Differential effects of anterior and posterior pedunculopontine tegmental nucleus lesions on intravenous self-administration of nicotine, *2004 Abstract Viewer/Itinerary Planner*, Society for Neuroscience, Washington D.C., Program no. 575.3.

Allen, L.F. and Winn, P., 1995, Excitotoxic lesions of the pedunculopontine tegmental nucleus disinhibit orofacial behaviours stimulated by microinjections of d-amphetamine into the rat ventrolateral caudate-putamen, *Exp. Brain. Res*. **104**:262.

Bechara, A. and van der Kooy, D., 1989, The tegmental pedunculopontine nucleus: a brain-stem output of the limbic system critical for the conditioned place preferences produced by morphine and amphetamine, *J. Neurosci.* **9**:3400.

Bechara, A., Harrington, F., Nader, K. and van der Kooy, D., 1992, Neurobiology of motivation: double dissociation of two motivational mechanisms mediating opiate reward in drug-naïve versus drug-dependent animals, *Behav. Neurosci.* **106**:798.

Bechara, A. and van der Kooy, D., 1992a, A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats, *Behav. Neurosci.* **106**:351

Bechara, A. and van der Kooy, D., 1992b, Chronic exposure to morphine does not alter the neural tissues subserving its acute rewarding properties: apparent tolerance is overshadowing, *Behav. Neurosci.* **106**:364.

Bechara, A., Nader K. and van der Kooy, D., 1998, A two-separate motivational systems hypothesis of opioid addiction, *Pharm. Biochem. Behav.* **59**:1.

Beninato, M. and Spencer, R.F., 1986, A cholinergic projection to the rat superior colliculus demonstrated by retrograde transport of horseradish peroxidase and choline acetyltransferase immunohistochemistry. *J Comp. Neurol*. **253**: 525.

Berridge, K.C., and Robinson, T.E., 1998, What is the role of dopamine in reward: hedonic impact, reward learning or incentive salience? *Brain Res. Rev*. **28**: 309.

Bevan, M.D. and Bolam, J.P., 1995, Cholinergic, GABAergic and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat, *J. Neurosci.* **15**:7105.

Blaha, C. D. and Winn, P, 1993, Modulation of do[amine efflux in the striatum following cholinergic stimulation of the substantia nigra in intact and pedunculopontine tegmental nucleus-lesioned rats, *J. Neurosci.* **13**:1035.

Blaha, C.D., Allen, L.F., Das, S., Inglis, W.L., Latimer, M.P., Vincent, S.R. and Winn, P., 1996, Dopamine efflux in the nucleus accumbens following cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned and laterodorsal tegmental nucleus-lesioned rats, *J. Neurosci*. **16**:714.

Bolam, J.P., Francis, C.M. and Henderson, Z., 1991, Cholinergic input to dopaminergic neurons in the substantia nigra: a double immunocytochemical study, *Neurosci.* **41**:483.

Brantley, R.K. and Bass, A.H., 1988, Cholinergic neurons in the brain of a teleost fish (Porichthys notatus) located with a monoclonal antibody to choline acetyltransferase, *J. Comp. Neurol.* **275**:87.

Charara, A., Smith, Y. and Parent, A., 1996, Glutamatergic inputs from the pedunculopontine nucleus to midbrain dopaminergic neurons in primates: *Phaseolus vulgaris*-leucoagglutinin anterograde labeling combined with postembedding glutamate and GABA immunohistochemistry, *J. Comp. Neurol.* **364**:254.

Corrigall, W.A., Coen, K.M. and Adamson, K.L., 1994, Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area, *Brain Res.* **653**:278.

Corrigall, W.A., Coen, K.M., Adamson, K.L. and Chow, B.L.C., 1999, Manipulations of mu-opioid and nicotinic cholinergic receptors in the pontine tegmental region alter cocaine self-administration, *Psychopharm.* **145**:412.

Corrigall, W.A., Coen, K.M., Zhang, J., and Adamson, K.L., 2001, GABA mechanisms in the pedunculopontine tegmental nucleus influence particular aspects of nicotine self-administration selectively in the rat, *Psychopharm.* **158**:190.

Corrigall, W.A., Coen, K.M., Zhang, J., and Adamson, K.L.,, 2002, Pharmacological manipulations of the pedunculopontine tegmental nucleus in the rat reduce self-administration of both nicotine and cocaine, *Psychopharm.* **160**:198.

Dormont, J.F., Condé, H. and Farin, D., 1998, The role of the pedunculopontine tegmental nucleus in relation to conditioned motor performance in the cat. I. Context-dependent and reinforcement-related single unit activity, *Exp. Brain Res.* **121**: 401.

Erro, W., Lanciego, J.L. and Giminéz-Amaya, J.M., 1999, Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study, *Exp. Brain Res.* **127**:162.

Fay, R.A. and Norgren, R., 1997, Identification of rat brainstem multisynaptic connections to the oral motor nuclei using pseudorabies virus. I. Masticatory muscle motor systems, *Brain Res. Rev.* **25**:255.

Floresco, S.B., West, A.R., Ash, B., Moore, H. and Grace A.A., 2003, Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission, *Nat. Neurosci.* **6**:968.

Ford, B., Holmes, C.J., Mainville, L. and Jones, B.E., 1995, GABAergic neurons in the rat pontomesencephalic tegmentum: codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus, *J. Comp. Neurol.* **363**: 177.

Forster, G.L. and Blaha, C.D., 2003, Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat, *E. J. Neurosci.* **17**:751.

Hazrati, L.N. and Parent, A., 1992, Projection from the deep cerebellar nuclei to the pedunculopontine nucleus in the squirrel monkey, *Brain Res*. **585**:267.

Honda, T. and Semba, K., 1994, Serotonergic synaptic input to cholinergic neurons in the rat mesopontine tegmentum, *Brain Res.* **647**:299.

Inglis, W.L. and Winn P., 1995, The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation, *Prog. Neurobiol.* **47**:1.

Inglis, W.L., Dunbar, J.S. and Winn, P., 1994, Outflow from the nucleus accumbens to the pedunculopontine tegmental nucleus: dissociation between locomotor activity and the acquisition of responding for conditioned reinforcement stimulated by *d*-amphetamine, *Neurosci.* **62**:51.

Inglis, W.L., Olmstead, M.C. and Robbins, T.W., 2000, Pedunculopontine tegmental nucleus lesions impair stimulus-reward learning in autoshaping and conditioned reinforcement paradigms, *Behav. Neurosci.* **114**:285.

Jones, B.E., 1990, Immunohistochemical study of choline acetyltransferase-immunoreactive processes and cells innervating the pontomedullary reticular formation in the rat, *J. Comp. Neurol.* **295**:485.

Keating, G.L., Walker, S.C. and Winn, P., 2002, An examination of the effects of bilateral excitotoxic lesions of the pedunculopontine tegmental nucleus on responding to sucrose reward, *Behav. Brain Res.* **134**:217.

Kobayashi, S. and Nakamura, Y., 2003, Synaptic organization of the rat parafascicular nucleus, with special reference to its afferents from the superior colliculus and the pedunculopontine tegmental nucleus, *Brain Res.* **980**:80.

Leonard, C.S. and Llinás, L,L., 1990, Electrophysiology of mammalian pedunculopontine and laterodorsal tegmental neurons in vitro: implications for the control of REM sleep, in: *Brain Cholinergic Systems* Steriade, M. and Biesold, D., eds., Oxford University Press, Oxford, pp205-223.

Marin, O., Smeets, W.J.A.J. and González, A., 1998 Evolution of the basal ganglia in tetrapods: a new perspective based on recent studies in amphibians, *Trends Neurosci.* **21**:487.

Mena-Segovia, J., Bolam, J.P. and Magill, P.J., 2004, Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci.* **27**: 565.

Mesulam, M.M., Mufson, E.J., Wainer, B.H. and Levey A.I., 1983, Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6), *Neurosci.* **10**:1185.

Mesulam, M.M., Geula, C., Bothwell, M.A. and Hersh, L.B., 1989, Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons, *J. Comp. Neurol.* **281**:611.

Moriizumi, T. and Hattori, T., 1992, Separate neuronal projections of the rat globus pallidus projecting to the subthalamic nucleus, auditory cortex and pedunculopontine tegmental area, *Neurosci.* **46**:701.

Nauta, W.J.H., Mehler, W.R., 1966, Projections of the lentiform nuclei in the monkey, *Brain Res.* **1**:3.

Oakman S.A., Faris, P.L., Kerr, P.E., Cozzari, C. and Hartman B.K., 1995, Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area, *J. Neurosci.* **15**:5859.

Olmstead, M.C. and Franklin, K.B.J., 1994, Lesions of the pedunculopontine tegmental nucleus block drug-induced reinforcement but not amphetamine-induced locomotion, *Brain Res.* **638**:29.

Olmstead, M.C., Inglis, W.L., Bordeaux, C.P., Clarke, E.J., Wallum, N.P., Everitt, B.J. and Robbins T.W., 1999, Lesions of the pedunculopontine tegmental nucleus increase sucrose consumption but do not affect discrimination or contrast effects, *Behav. Neurosci.* **113**:732.

Pahapill, P.A. and Lozano, A.M., 2000, The pedunculopontine nucleus and Parkinson's disease, *Brain* **123**:1767.

Parent, M. and Parent, A., 2004, The pallidofugal motor system in primates, *Parkinson's Rel. Disord.* **10**:203.

Parker, J.L. and van der Kooy, D., 1995, Tegmental pedunculopontine nucleus lesions do not block cocaine reward, *Pharm. Biochem. Behav.* **52**:77.

Paxinos, G. and Watson, C., 1997, *The Rat Brain In Stereotaxic Co-ordinates*, Academic Press, New York.

Redgrave, P., Mitchell, I.J., and Dean, P., 1987, Further evidence for segregated output channels from superior colliculus in rat: ipsilateral tecto-pontine and tecto-cuneiform projections have different cells of origin, *Brain Res.* **413**: 170.

Saitoh, K., Hattori, S., Song, W-.J., Isa, T. and Takakusaki, K., 2003, Nigral GABAergic inhibition upon cholinergic neurons in the rat pedunculopontine tegmental nucleus, *Eur. J. Neurosci.* **18**:879.

Schultz, W., 2002, Getting formal with dopamine and reward, *Neuron* **36**: 241.

Skinner, R.D., Kinjo, N., Henderson, V. and Garcia-Rill, E., 1990 Locomotor projections from the pedunculopontine tegmental nucleus to the spinal cord, *NeuroReport* **1**:183.

Semba, K., Reiner, P.B. and Fibiger, H.C., 1990, Single cholinergic mesopontine tegmental neurons project to both the pontine reticular formation and the thalamus in the rat, *Neurosci.* **38**:643.

Takakusaki, K., Shiroyama, T. and Kitai, S.T., 1997, Two types of cholinergic neurons in the rat tegmental pedunculopontine nucleus: electrophysiological and morphological characterization, *Neurosci.* **79**:1089.

Usunoff, K.G., Kharazia, V.N., Valtschanoff, J.G., Schmidt, H.H. and Weinberg, R.J., 1999, Nitric oxide synthase-containing projections to the ventrobasal thalamus in the rat, *Anat. Embryol.* **200**:265.

Vincent, S.R. and Kimura, H., 1992, Histochemical mapping of nitric oxide synthase in the rat brain, *Neurosci.* **46**:755.

Vincent, S.R., Satoh, K., Armstrong, D.M., Panula, P., Vale, W. and Fibiger H.C., 1986, Neuropeptides and NADPH-diaphorase activity in the ascending cholinergic reticular system of the rat, *Neurosci.* **17**:167.

Williams, J.A. and Reiner, P.B., 1993, Noradrenaline hyperpolarizes identified rat mesopontine cholinergic neurons in vitro, *J. Neurosci.* **13**:3878.

Zahm, D.S., Williams, E.A., Latimer, M.P. and Winn, P, 2001,. Ventral mesopontine projections of the caudomedial shell of the nucleus accumbens and extended amygdala in the rat: double dissociation by organization and development, *J. Comp. Neurol.* **436**:111.