SWS promoting MHB-IPN-MRN circuit opposes
the theta promoting circuit, active wake and REM sleep.

Karin Vadovičová,
Neuroradiology Department, Brescia University, Brescia, Italy

ABSTRACT The multisynaptic axonal tracts between hippocampus and medial habenula (MHB) observed in my DTI study using probabilistic tractography made me explore their connectivity. Found tract linked hippocampus to septum, and amygdala to bed nucleus of stria terminalis (BNST). Axons from septum and BNST passed by anteromedial thalamic nucleus (AM) to MHB, and from MHB to pineal gland, linked to control of circadian cycles and sleep. Combination of known findings about septum and MHB connectivity and function led to idea that posterior septum activates MHB, leading to activation of IPN, MRN and serotonin release. This MHB-IPN-MRN circuit promotes slow wave sleep (SWS), high serotonin and low acetylcholine state. This SWS promoting circuit reciprocally suppresses the theta oscillations promoting circuit, linked to high acetylcholine in brain, and formed by supramamillary area (SUM) projections to the medial septum (MS) that activates hippocampus or other theta-coupled regions. The MHB pathway inhibits, possibly reciprocally also some stimulating input to theta-generating SUM and MS, from wake-on nucleus incertus (NI), posterior hypothalamus (PH) and laterodorsal tegmentum (LDT) neurons, and REM-on reticular nucleus pontis oralis (PnO). So the SWS- promoting circuit attenuates theta and both active wake state and REM sleep promoting regions. As the theta in wake state is linked to recording and binding information with their spatio-temporal and relational context by hippocampus, while the SWS supports replay of hippocampally stored information/memory trace and its cortical reactivation, e. g. in retrosplenial cortex linked to autobiographic memory or in prefrontal cortex that can combine any information.

Introduction.
Serotonin signal induces (behavioural and emotional) relaxation, slow-down and rest while dopamine promotes action, locomotion, speeding up. Serotonin is present early during embryogenesis, probably to slow down or suppress the heart rate by attenuating sympathetic system. Later on the same serotonin slows down skeletal muscles movement (running, locomotion) and breathing, plus might enable the relaxation phase in ON-OFF rhythmic motor activity of axial muscles in fish where alternates contraction and extension. Brain serotonin slows down locomotion, calms down the active avoidance, negative emotions and drive, makes us rest and relax, promotes well-being (Vadovičova and Gasparotti, 2014), satisfaction and reconstructive (deep) stage of sleep called slow wave sleep or non-REM (SWS or NREM) sleep. SWS has high amplitude, low frequency EEG, while rapid eye movement (REM) sleep has low amplitude, high frequency EEG oscillations (Jouvet, 1962). The SWS is known for its recovery-restorative function, calcium cascade of nocturnal proteosyntesis and also for the replay and
transfer of contextually/relationally bound information from the hippocampus to cortex, by replaying the waking neuronal firing patterns in hippocampus and cortex during temporally coupled hippocampal sharp-wave/ripples (SWRs) and cortical spindles (Buzsaki, 1989). The 5-10 Hz oscillations in the hippocampal local field potential called theta rhythm occur during voluntary exploration, locomotion and REM sleep (O'Keefe and Recce, 1993; Bland and Oddie, 2001; Buzsaki, 2002). REM sleep is proportionally more abundant in young mammals (Roffwarg et al. 1966). The EEG patterns of sleep and wakefulness become adult-like only after full development of the cortex (Blumberg et al., 2003). The fast EEG synchrony typical of wakefulness develops through adolescence in humans, similarly to prolonged cortical maturation in higher primates (Uhlhaas et al., 2009).

Serotonin from DRN has been functionally grouped with the arousal-promoting neuromodulators important for wake state: noradrenaline, histamine, orexin (hypocretin) and acetylcholine system. Orexin stabilizes wakefulness, as its deficiency causes narcolepsy disorder with inability to maintain long waking periods, with abrupt transitions into SWS sleep, and intrusions of REM sleep into waking (Sakurai, 2007). In addition, the mice deficient in norepinephrine or histamin sleep more and have no trouble to fall asleep after mild stress. In contrary, mice lacking serotonin receptor 5-HT1A (inhibitory receptor, also MRN autoreceptor) have 400% more REM sleep. The orexin, histamine and noradrenaline neurons have highest firing rate in wakefulness (Aston-Jones and Bloom, 1981). Extracellular electrophysiological recordings in freely moving cats have shown that DRN serotonergic neurons fire tonically during wakefulness, decrease their activity during slow wave sleep (SWS), and are nearly quiescent during REM (McGinty and Harper, 1976; Trulson and Jacobs, 1979). In contrary, the acetylcholine levels in the rat thalamus (innervated by mesopontine cholinergic neurons) are intermediate in SWS but high in both REM and wake-state (Williams et al., 1994). In addition the acetylcholine release during active waking is increased by approximately 75% compared to quiet waking (Marrosu et al., 1995). Interestingly the tonic dopamine firing seems to be present in all sleep-wake cycles, and burst firing was found in both wake and REM sleep (Dahan et al., 2007).

Raphe system lesion in cats caused permanent insomnia and diminution of cerebral serotonin (Jouvet et al., 1967) and MRN lesions produced uninterrupted theta (Maru et al., 1979; Yamamoto et al., 1979). Inhibition of serotonin synthesis in cats induces PGO waves in waking state (Jacobs et al., 1972). Serotonergic firing is inversely correlated with PGO waves occurrence (Lydic et al., 1983). Injection of serotonin precursor induced SWS and suppressed REM for 5-6 hours (Bogdanski et al., 1958; Monnier and Tissor, 1958; Costa et al, 1960; Delorme, 1966). So these SWS-promoting effects of serotonin were not caused by wakefulness linked DRN and its cortical, striatal and amygdalar projections linked to choice behavior and well-being, but by MRN that has the needed subcortical afferents and efferents to interact with other SWS promoting regions, and to suppress the theta, wake and REM sleep promoting regions. Main MRN efferents target midline forebrain including SUM, medial mamillary body (MMB), MS/vDBB, PH, lateral habenula (LHb), perifornical hypothalamus PeF, midline and intralaminar thalamus, zona incerta (ZI) and hippocampus (Vertes and Linley, 2008), while main MRN and DRN afferents are from lateral and medial preoptic
area (LPO, MPO), LHb, lateral hypothalamus (LH), PeF (both produce orexin) and
dorsomedial nuclei of hypothalamus (DMN), midbrain nuclei, locus coerulues
(LC), caudal raphe nuclei, LDT and PAG. Additional MRN afferents are from
interpeduncular nucleus (IPN) and MB, while the DRN afferents are from
amygdala, BNST, lateral septum (LS), substantia nigra, diagonal band of Broca
(DBB) and tuberomamyillary nucleus (TMN). Serotonin hyperpolarizes cholinergic
burst neurons in the rat LDT in vitro (Luebke et al., 1992), so opposes the theta
circuit, wake and REM states that require acetylcholine signal. Serotonergic MRN
projections inhibit also theta bursting of MS/vDBB, the source of hippocampal
theta rhythm (Kinney et al., 1996). This was found by recordings in mice MS/DBB
and hippocampus after inhibition of MRN by 5-HT1A agonist on its autoreceptors.
This is a functional evidence for antagonism between the SWS-provoking MRN
and theta-generating MS/vDBB region.

Based on functional studies and the anatomical connectivity of medial habenula
(MHb), interpeduncular nucleus (IPN) and serotonergic MRN, I will show the role
of the MHb → IPN → MRN circuit (linked to the low acetylcholine state) in
promoting SWS. I propose the antagonism (reciprocal inhibition) between this
SWS-promoting circuit and the theta- promoting circuit, which increases temporal
coupling in both the active wake and REM sleep, linked to high acetylcholine
states in brain. So I will show the opposition and reciprocal inhibition between the
MHb-IPN-MRN circuit and LPO versus the SUM-MS/vDBB, NI, PH, VTg and LDT.

MHb, IPN and MRN connectivity

I wish to provide wider context, circuit based and functional evidence for the idea
that posterior septum (PS) activates MHb that activates IPN that stimulates
serotonergic MRN, to promote SWS and to inhibit theta promoting regions
(Vadovičova, 2014). The idea came from DTI probabilistic tractography results in
humans that showed disynaptic axonal tract connecting hippocampus and
amygdala to septum and anterior BNST. The tract passed tightly by both septum
and aBNST, then turned posteriorly by anteromedial thalamus (AM), reached via
stria medialis to MHb, and from MHb to the pineal gland. This pathway resembled
the MHb afferents known from rats tracing studies. The tract branched around
septum and BNST to reach hypothalamus, and via the amygdalofugal pathway
(via substantia innominata, SI) also the dorsal CeA and hippocampus. Also vACC
had axonal links to septum and BNST. Now we need to look back into anatomy
and physiology data to see what the diverse septo-habenular projections do.

Medial habenula, MHb

The main MHb input comes from supracommissural septum (Herkenham and
Nauta, 1977). Triangular septum (TS) with input from hippocampal dentate gyrus;
and septofimbrial nucleus (SF) with input from fimbria of hippocampus form
posterior septum (PS) and project to MHb (Raisman, 1966). The MHb receives
input from the glutamatergic and ATPergic triangular septum, from cholinergic
septofimbrial nuclei, from GABAergic medial septum and vertical DBB (MS/vDBB),
serotonergic raphe, noradrenergic locus coerulues neurons and sympathetic
superior cervical ganglion, from substance P-ergic anterior medial part of BNST
(amBNST or BAC, bed nucleus of anterior commissure), and from dopaminergic
VTA (Herkenham and Nauta, 1977; Gottesfeld, 1983; Qin and Luo, 2009;
MHb has also afferents from LDT, and reciprocal connections with MS/vDBB (Woolf, 1991), which I suggest are all inhibitory. I propose that triangular and septofimbrial septal nuclei stimulate MHb, while the MS/vDBB and noradrenergic LC and sympathetic system neurons attenuate MHb output. The theta-generating MS/DBB inhibits MHb because MHb via IPN stimulates serotonergic MRN that promotes SWS and suppresses few regions of theta-promoting circuit: SUM, MS/vDBB and LDT. Similarly, the stress (and light) evoked noradrenaline (NA) input suppresses MHb pathway to interrupt or postpone induction of SWS in unsafe circumstances. In addition the substance P likely activates MHb when the circumstances are safe enough to afford sleep (without imminent threat). This is supported by TS and aBNST/BAC, connectivity that forms two parallel pathways: dentate gyrus → TS → vMHb → IPN core, and the MeA → BAC → dMHb → lateral IPN (Yamaguchi et al., 2013) and by increased fear and arousal after BAC lesions. In addition the BAC input is from the anxiety decreasing medial amygdala (MeA). The amBNST/BAC might also attenuate SUM, LC, VTA, SI, PVT, PAG, CeA; and besides the MHb also stimulate LPO. The superior MHb is glutamatergic and also expresses Interleukin-18 (IL-18); the dorsal MHb is both glutamatergic and substance P-ergic; both the superior and dorsal MHb have high density of μ-opioid receptor; while the inferior parts of MHb are both cholinergic and glutamatergic (Aizawa et al., 2012; Sugama et al., 2002). MHb sends topographically organized glutamate, substance P and acetylcholine output to IPN (Qin and Luo, 2009; Ren et al., 2011; Herkenham and Nauta, 1979). Substance P from MHb projections were found to the LHB (Kim and Chang, 2005; Antolin-Fontes et al., 2015) and VTA (Claudio Cuello et al., 1978). The Mhb projects to IPN via the internal part of fasciculus retroflexus and via IPN it controls MRN, LPO and LDT (Herkenham and Nauta, 1979; Groenewegen et al., 1986).

Based on its anatomical connectivity and interactions with neuromodulators, I propose that MHb stimulates SWS via the MHb → IPN → MRN pathway that also suppresses the theta, alertness and REM driving regions. This is supported by dense mu opioid receptors (binding morphine) and circadian rhythmicity of MHb neurons (McCormick and Prince, 1987; Quick et al., 1999; Guiding and Piggins, 2007), by the markedly increased MHb and IPN metabolic activity during anesthesia (pentobarbital, ether and chloral hydrate) in rats (Herkenham, 1981), by the fact that the MHb neurons produce sleep promoting interleukin IL-18 (Sugama et al., 2002) and control via IPN the MRN serotonin. Further evidence comes from high firing rates of MRN cells in SWS and non-exploratory waking states in rats (when not recording new information in hippocampus), and their low firing rates during theta linked exploration and REM sleep (Jacobs and...
Azmitia, 1992; Marrosu et al., 1996). Firing of serotonergic DRN neurons is high in wakefulness, lower in SWS and minimal in REM sleep (Saper et al., 2001). The cholinergic activity in LDT/PPT and acetylcholine levels at cortex and hippocampus are high at wake and REM sleep (Sakai, 1980; Marrosu et al., 1995). Noradrenergic LC neurons discharge rate is highest during active waking, significantly lower during quiet waking, and ceased during SWS and REM sleep (Takahashi et al., 2010). Earlier studies found also lower (than wake) LC firing in SWS in rats (Aston-Jones and Bloom, 1981) but lack of NA in SWS fits its alarm/alert inducing function. Histamine neurons of TMN in posterior hypothalamus (PH) are active only in wakefulness, highest at high vigilance, low at quiet waking and silent during SWS and REM (Takahashi et al., 2006).

Wake, SWS and REM circuits (ON and OFF regions)

The LPO or ventrolateral preoptic area (VLPO) induces SWS by inhibiting cholinergic LDT/PPT and BNM (source of cortical stimulation and gamma coupling, inhibited by adenosine), noradrenergic LC, histaminergic TMN in PH, orexinergic LH and serotonergic DRN, so the wake-promoting monoaminergic arousal system (Strecker et al., 2000). Reciprocally the TMN, LC, orexinergic LH and GABAergic BNM inhibit VLPO, either directly or via interneurons (Steininger et al., 2001). LDT/PPT and LH/orexin stimulate cholinergic and parvalbumin containing BNM that induces fast gamma coupling in cortex (Kim et al., 2015), moreover orexin stabilizes wakefulness by exciting cortex, TMN, LC, DRN, VTA and LDT/PPT (Kilduff and Peyron, 2000; Saper et al., 2001, Bernard et al., 2002). In addition the serotonergic and noradrenergic (REM-off) regions are suppressed by REM-promoting PnO, subcoerulear (SubC) or medullar dorsal paragigantocellular nuclei (DPGi), directly or via nearby GABAergic REM-on neurons (Gervasoni et al., 1998 and 2000). reciprocally, the LC and DRN inactivation increased REM sleep (Cespuglio et al., 1982). Noradrenaline inhibited mesopontine cholinergic neurons (Williams and Reiner, 1993), while serotonin injection into SubC in rats suppressed PGO waves in pons without affecting thalamic or cortical PGO (Datta et al., 2003). REM-on LDT/PPT neurons were inhibited by 5-HT 1A agonist in cats while wake/REM-on neurons not (Thakkar et al., 1998). Also the SWS inducing LPO is inhibited by REM-on nuclei that stimulate GABA (REM-on) neurons by LPO. SWS-on deep mesencephalic reticular (also named LPT) and wake-on locomotion facilitating (motor neurons stimulating) vIPAG nuclei also inhibit REM-on regions SubC and PnO/RPO, while PnO is stimulated by REM-on neurons of PPT/LDT.

So I predict reciprocally inhibitory interaction between the SWS promoting MHb → IPN → MRN pathway and LPO output versus the activation of the theta-promoting circuit SUM → MS/vDBB → hippocampus. I propose also opposition between the MHb-pathway activation and the activity of regions that stimulate the theta-generating circuit: Ni, VTg, LDT and histaminergic PH; and some wakefulness promoting regions: TMN, orexinergic LH, gamma inducing NBM, value-signaling/action-urging VTA, and alert linked LC. So there is also opposition (mutual inhibition) between the SWS promoting circuit (PS-MHb-IPN-MRN, and LPO) and the wake promoting orexin, histamine, noradrenaline and locomotion triggering dopamine systems. SWS-promoting circuit might show similar opposition with regions of the REM-promoting circuits, PnO, PnC or SubC.
Theta circuit connectivity with the MHb-pathway:

Theta oscillations in hippocampus occur in awake exploration and in REM sleep (Vanderwolf, 1969). They are generated by supramamillary nuclei (SUM) activation of medial septum and vertical limb of diagonal band of Broca (MD/vDBB) that induce theta in hippocampus and other target regions. The SUM is activated by multisynaptic input (PnO/RPO) in anesthetized rats in REM (Vertes and Martin, 1988; Vertes and Kocsis, 1997; Oddie et al., 1994), possibly via LDT/PPT, by nucleus incertus (NI), posterior hypothalamus (PH), or dopaminergic input to SUM in waking state; and by NI activation of MS by relaxin-3 (Ma et al., 2009). Another way to induce theta coupling in brain might be via prefrontal input to SUM. SUM and MS are via medial mamillary body connected with the VTg that (similar to SUM, MMB and MS) shows theta oscillations. Hippocampus has efferents from subiculum via fornix to septum, anterior thalamus (ATN) and mamillary body, and MB projects to ATN (Aggleton et al., 2005).

Supramamillary nucleus, SUM

SUM controls the frequency of hippocampal theta activity via MS/DBB, while MS/vDBB controls its amplitude. SUM is known to stimulate theta rhythm during exploration in rats (Vertes and Kocsis, 1997) that gets disrupted by serotonergic MRN. SUM in rats has reciprocal connection with MMB, VTg, PH, LH, AH, LDT, MS/DBB, LS, PAG, LPO, MPO, MRN, DRN, VTA (expected value signal), cognitive anterior cingulate cortex (homologue of human cognitive PFC) and reward/value coding in medial and ventrolateral orbital cortex. SUM afferents come also from IPN, LHb (Kiss et al., 2002), VMH, BNST, subiculum and nucleus prepositus. SUM efferents go also to anteromedial and anteroventral thalamus (AM, AV), reuniens nuclei, intralaminar thalamic, CM, MDT, SI (SI includes primate BNM homologue), hippocampus, dentate gyrus (strongly), entorhinal cortex (EC), frontal cortex, subthalamic nucleus (STN), amygdala, LC and cerebellar nuclei (CN), (Vertes, 1988, 1992; Hayakawa et al., 1993; Shibata, 1987; Risold and Swanson, 1997; Swanson, 1982; Thinschmidt, 1993; Kiss et al., 2002, Contestabile and Flumerfelt, 1981). So I propose stimulating input to SUM from wake promoting PH, LH, LDT (also from wake/REM-on LDT cells), from VTA with its value-signaling dopamine, from PAG; and cortex. I propose inhibitory input from LHb, and from SWS- promoting IPN, MRN and LPO to SUM. Similarly I suggest stimulatory efferents from SUM to VTg, AM, AV, CM, MDT, SI, amygdala, EC, CN, and inhibitory efferents to MRN.

Ventrotegmental nucleus of Gudden, VTg and DTg

VTg has reciprocal projections with MMB, and input from prefrontal, cingulate, insular and retrosplenial cortex, MRN, IPN, LHb, maybe even from BNM, PH, LH and LPO as VTg receives input from basal forebrain and hypothalamus (Irle et al., 1984). Both VTg and SUM receive LHb, IPN and MRN projections, so my prediction is that they are inhibitory. Because the VTg is needed for alternate choice working memory and during mental navigation tasks, but not during SWS sleep. In addition the VTg has possibly stimulating input from DTg, vestibular nucleus (head movement signal), SNc (informational value signal, what way of doing
things is right), VTA (expected reward value signal), LC (alarm signal), PAG (fear response) and dopaminergic cells in zona incerta (ZI). VTg has input also from fields of Forel, nucleus of Darkschewitsch (reflex gaze), interstitial nucleus of Cajal (integration of head and eye movements) and nucleus prepositus hypoglossi. Many MMB projecting VTg neurons are parvalbumin positive, so capable to transfer fast gamma oscillations important for WM.

Triangular and septofimbrial septal nuclei, TS and SF.

TS projects to MHB, IPN and LHb (Raisman, 1966). Posterioro septum (TS and SF) has GABAergic projections to NI (and NI to PS), SUM and MRN, while horizontal DBB (hDBB) has GABAergic projections to NI (Sanchez-Perez et al., 2015). By proposing SWS promoting role of PS, I suggest that TS inhibits LHb to disinhibit the MRN, and that TS and SF inhibit NI and SUM, but activate MRN (by inhibiting MRN interneurons). NI is known to induce theta by its relaxin-3 release in MS (Ma et al., 2009). Horizontal DBB together with NBM are the main source of the cortical cholinergic innervation and parvalbumin GABA projections that induce fast gamma rhythm linked to attention and temporal summation. So I suggest that hDBB induces gamma oscillations in NI towards informative and salient stimuli to increase temporal coupling (and temporal summation) towards important information.

Median raphe nucleus, MRN

Major MRN input is from IPN, LHb, MS, MB, LPO, MPO, LH, perifornical hypothalamus, DMN, PAG, LDT, LC and infralimbic cortex (vACC homologue). Medial LHb reciprocally inhibits MRN (Wang and Aghajanian, 1977). MRN projects to medial mammillary body (MMB), SUM, PH, perifornical hypothalamus (PF/LH), cholinergic MS/vDBB, hDBB, NBM, septum, VTA, dopaminergic A13 region of ZI, LHb, IPN, MPO, reuniens nucleus, mediodorsal (MDT), central medial (CM), paracentral and central lateral nuclei of midline, intralaminar thalamus, suprachiasmatic nucleus (SCN), hippocampus and NAc (Vertes and Martin, 1998, Vertes and Linley, 2008). Cortical projections are light and restricted to perirhinal, entorhinal and some prefrontal cortex. MRN stimulation enhances the secretion of gonadotropins (James et al., 1987). Glutamate input to MRN was increased during non-theta phase of anesthesia in rats but not after tail pinch (Varga et al., 1998). This evidence supports proposed activation of MRN by MHB in SWS, as MHB is also stimulated by anesthetics, possibly disinhibited by morfin, and has indirect input to MRN via IPN. So I predict that MHB stimulates IPN, which stimulates MRN to release serotonin during SWS. Both LPO and MRN promote SWS and suppress parts of cholinergic theta-promoting circuit. So I propose that LPO and possibly vACC activate MRN, while the MS/vDBB, MMB, LDT, orexinergic LH, noradrenergic LC, and PAG inhibit MRN. Similarly to the known MRN inhibition of SUM, I suggest that MRN attenuates also these theta- , working memory and arousal linked regions: MMB, MS/vDBB, histaminergic PH, orexinergic LH, VTA, A13 of ZI, intralaminar and midline thalamic nuclei. Hippocampal theta induced by SUM and MS activation was produced after MRN inhibition by glutamatergic antagonists, GABA agonist and serotonin 1A agonist (acting via MRN
autoreceptor) in urethane anesthetized rats (Kinney et al., 1994; Kinney et al., 1995; Vertes et al, 1994, Kinney et al., 1996).

Interpeduncular nucleus, IPN

Main IPN input comes from MHB, less from medial LHb, MPO, ventral hypothalamus, MRN, DRN, dorsal and ventral tegmental nuclei of Gudden (DTg, VTg), LDT, PAG, SUM, premamillary nuclei, LC, sparse from hDBB (Contestabile and Flumerfelt, 1981; Vertes and Fass, 1988), and some from VTA neurons that contain dopamine and corticotropin releasing factor (CRF), (Zhao-Shea et al., 2013). IPN neurons are mostly GABAergic and project to MRN, DRN, LPO, MPO, LDT, DTg and VTg (strongly), medial mamillary body (MMB, weakly), NI, basal nucleus of Meynert (BNM), LC, PAG, MS/DBB, LH, hypothalamus, entorhinal cortex (EC), hippocampus, MDT, nucleus gelatinosus, and midline thalamic nuclei (Groenewegen et al., 1986; Goto et al., 2001; Vertes and Fass, 1988). LDT has reciprocal connections with IPN, but also with MRN and LPO. So it is possible that IPN, MRN and LPO attenuate LDT output, to promote SWS. As BNM induces cortical gamma (300 Hz) oscillations and wakefulness (Brown and McKenna, 2015), while the VTg shows theta oscillations, contains fast firing parvalbumin GABA neurons involved in gamma oscillations VTg, and is needed in alternation task working memory (Dillingham et al., 2015), I suggest an inhibitory effect of IPN on NBM and VTg. I propose that IPN stimulates the SWS-promoting LPO and MRN serotonin release; but attenuates the output of theta and arousal promoting regions: DTg, MB, NI, LDT, BNM, LC and fight-or-flight response of PAG. In addition the medial LHb that inhibits MRN possibly inhibits also IPN (by targeting IPN interneurons) and is itself inhibited by MHB. The IPN interneurons might be targeted also by dopamine and CRH release from VTA to interrupt sleep. Similarly, the IPN is probably inhibited by DTg, VTg, LDT, PAG, hDBB, SUM, premamillary nuclei and LC.

Nucleus incertus, NI

The NI is known to induce theta rhythm and increase spatial working memory performance (and theta-power in hippocampus), by releasing peptide relaxin-3 into MS/DBB (Ma et al, 2009). Even in MS of anaesthetised rats did the relaxin-3 antagonist decreased PnO-induced hippocampal theta power (Ma et al, 2009). NI in rats has reciprocal connections with cortical affective evaluation regions: prelimbic (homologue of dACC in primates), medial and ventrolateral orbital cortex; with cognitive anterior cingulate cortex (cognitive PFC homologue); autobiographic memory in RSC; subcortical MRN, IPN (Goto et al., 2001; Aizawa et al., 2012), LPO, ZI, medial LHb, SUM, PH, LH, ventrolateral PAG, MS/vDBB (GABAAergic negative feedback) and pontine reticular nucleus. Medial LHb inhibits MRN and projects to intermediate part of the IPN (Wang and Aghajanian, 1977; 2015; Kim, 2009). I guess that the cortical input likely stimulates via NI the theta coupling to enhance the recording of episodes with affective or informative meaning to us. Based on the properties of SWS promoting circuit MHB-IPN-MRN, I predict that LHb and the theta state opposing IPN and MRN reciprocally inhibit
the output of the theta- and arousal inducing NI, and that LHb inhibits the IPN output to MRN.

The NI in rats and mice has receptors for CRH (corticotropin releasing hormone), orexin, MCH (melanin concentrating hormone, up in REM), oxytocin, serotonin 5-HT1A and ghrelin (Bittencourt and Sawchenko, 2000; Greco and Shiromani, 2001; Marcus et al., 2001; Saito et al., 2001; Vaccari et al., 1998; Mani et al, 2014; Miyamoto et al., 2008). So the MRN serotonin likely attenuates NI in SWS, while the wake linked agents activate NI to enforce theta coupling. I suggest that histaminergic and orexinergic neurons of PH/LH stimulate NI, as both also promote wakefulness, and that LPO inhibits NI, as LPO promotes SWS that opposes theta state and arousal. NI in rats also projects also to all hippocampus especially to dorsal fimbria and ventral dentate gyrus, CA3 and subiculum, entorhinal cortex, claustrum, SI, PPT, LS, SF, TS, BNST, MMB, LMB, DRN, PVT, PVN, DMN, VMN, MPO, SON, AH, arcuate nucleus, amygdala, MHB, CM, MDT, PVT, reuniens nucleus, AV, AM, AD, contralateral NI, NAc, ZI, VTA, SNc, NAc and SC (Goto et al., 2001; Olucha-Bordonau et al., 2003 and 2012; Teruel-Marti et al., 2008). I predict that NI (besides known effect on MS theta) activates its targets or strengthens their theta oscillations in PFC, RSC, hippocampus, BNST, LS, PAG, PVN, PVT, MDT and CM; but inhibits MHb, IPN, MRN and LPO.

GABAergic neurons in the VLPO promote sleep by inhibiting arousal-promoting circuits, such as TMN (Lydic and Baghdoyan, 2005). LPO was found to promote SWS. LPO projects to SUM, LDT and PPT, and based on their properties I propose that LPO inhibits them. This inhibition might be reciprocal. It was found that MRN serotonin inhibits LTD, PPT and SUM. LPO and LH project to LHb, RMTg and VTA. So I predict stimulatory effect of LPO on RMTg, and inhibitory effect of LPO on LHb and VTA, to disinhibit the MRN serotonin release (suppressed by medial LHb) but to inhibit the dopamine groups (SNc/A9, VTA/A10 and A11) that do facilitate locomotion, drive (go-for-it) and activate spinal motor neurons (A11). This claim is supported by robust locomotor activation after infusion of the GABA agonist muscimol into the RMTg (Lavezezi et al., 2014). Another supporting fact is that the LDT is essential for burst firing of VTA dopamine neurons (Lodge DJ, Grace AA, 2006). Stimulation of PPT or LDT excites dopaminergic neurons of VTA and SNc (Lacey et al. 1990) and is needed for maintenance of burst firing of dopamine neurons (Lodge and Grace, 2006). The RMTg is known for reciprocal connections with LDT, PPT, pontine and medullary reticular formation, and for strongly suppressing effect on VTA, SNc and DRN (Perroti et al., 2005; Jhau et al., 2009 a, b; Kaufling et al., 2009; Balcita-Pedicino et al., 2011). I propose that RMTg mutually suppresses LDT and PPT to decrease arousal and locomotion (e.g. after injuries, in sickness, in depression). So the LPO uses the LHb and RMTg as "switch off-switch on" buttons to enable SWS, by boosting the MRN serotonin system and suppressing SNc and VTA dopamine system. Actually the LPO might activate just that part of RMTg (lateral ?) that suppresses SNc and VTA, because the the serotonergic DRN firing is reduced during SWS but ceased only at REM. Interestingly respiratory rate is higher in REM sleep compared with both non-REM sleep and wakefulness, in line with the inhibition/cessation of serotonergic firing at MRN and DRN, and with its calming effect on respiration.

Similarly to the LPO, I guess also the SWS-on deep mesencephalic nuclei might suppress dopamine system. That population of BNST neurons, which promotes reactivity to threat, activates VTA and inhibits LPO, most probably inhibits also

Lateral preoptic area, LPO

GABAergic neurons in the VLPO promote sleep by inhibiting arousal-promoting circuits, such as TMN (Lydic and Baghdoyan, 2005). LPO was found to promote SWS. LPO projects to SUM, LDT and PPT, and based on their properties I propose that LPO inhibits them. This inhibition might be reciprocal. It was found that MRN serotonin inhibits LTD, PPT and SUM. LPO and LH project to LHb, RMTg and VTA. So I predict stimulatory effect of LPO on RMTg, and inhibitory effect of LPO on LHb and VTA, to disinhibit the MRN serotonin release (suppressed by medial LHb) but to inhibit the dopamine groups (SNc/A9, VTA/A10 and A11) that do facilitate locomotion, drive (go-for-it) and activate spinal motor neurons (A11). This claim is supported by robust locomotor activation after infusion of the GABA agonist muscimol into the RMTg (Lavezezi et al., 2014). Another supporting fact is that the LDT is essential for burst firing of VTA dopamine neurons (Lodge DJ, Grace AA, 2006). Stimulation of PPT or LDT excites dopaminergic neurons of VTA and SNc (Lacey et al. 1990) and is needed for maintenance of burst firing of dopamine neurons (Lodge and Grace, 2006). The RMTg is known for reciprocal connections with LDT, PPT, pontine and medullary reticular formation, and for strongly suppressing effect on VTA, SNc and DRN (Perroti et al., 2005; Jhau et al., 2009 a, b; Kaufling et al., 2009; Balcita-Pedicino et al., 2011). I propose that RMTg mutually suppresses LDT and PPT to decrease arousal and locomotion (e.g. after injuries, in sickness, in depression). So the LPO uses the LHb and RMTg as "switch off-switch on" buttons to enable SWS, by boosting the MRN serotonin system and suppressing SNc and VTA dopamine system. Actually the LPO might activate just that part of RMTg (lateral ?) that suppresses SNc and VTA, because the the serotonergic DRN firing is reduced during SWS but ceased only at REM. Interestingly respiratory rate is higher in REM sleep compared with both non-REM sleep and wakefulness, in line with the inhibition/cessation of serotonergic firing at MRN and DRN, and with its calming effect on respiration.

Similarly to the LPO, I guess also the SWS-on deep mesencephalic nuclei might suppress dopamine system. That population of BNST neurons, which promotes reactivity to threat, activates VTA and inhibits LPO, most probably inhibits also
the LHb and RMTg. Also the MS has input to LHb, RMTg and VTA, possible to induce there the theta coupling. I suggest inhibitory effect of LPO projections to SUM, to suppress theta during SWS. The main inhibitory input to LPO comes from GABAergic neurons of BNM, LS and BNST (Zahm et al., 1999, 2013; Zahm, 2006). Their role in fast gamma coupling, panic and anxiety response supports the LPO role in SWS, as threat suppresses SWS by inhibiting LPO, what leads to lower RMTg activity: causing rise in dopamine firing, agitation and impulsive response. Interestingly cholinergic projections from the mesopontine tegmentum inhibit the RMTg at muscarinic M4 receptors, while exciting VTA dopamine neurons at M5 receptors (Wasserman et al. 2013, 2014). So this acetylcholine might come from wake promoting LDT to disinhibit dopamine, to fuel motion, motivated behaviour, drive, reward and value/meaning based learning in wakefulness. The LPO projects also to reticular thalamic nucleus involved in up and down states in SWS, and to hippocampus, cortex and parabrachial nucleus, possibly to promote SWS sleep.

Lateral habenula, LHb

LHb directly and via RMTG activation strongly suppresses dopamine and serotonin (Christoph et al., 1986; Wang and Aghajanian, 1977; Park, 1987; Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). Looking at the previous section connectivity involving LHb, I came to conclusion that LHb might be used as a "switch-off" button to suppress serotonin (MRN and DRN) and lower dopamine (SNc, VTA) firing during REM.

Main LHb input is from GPi, LH, VTA, DRN, MRN, LPO, MS/vDBB, SI, NBM, PH, PAG and BNST (Herkenham and Nauta, 1977; Sutherland, 1982). LHb projects to SUM (Kiss et al., 2002), and medial LHb innervates intermediate IPN (Kim, 2009). LHb inhibits dopaminergic (VTA, SNc) and serotonergic (DRN, MRN); and stimulates GABAergic RMTg (Perroti et al., 2005; Jhou et al., 2009 a, b; Kaufling et al., 2009) that inhibits DRN, VTA and SNc. LHb projects also to LC, TMN, PH, LH, LDT, PPT, NBM, SI, MS/DBB, SUM, LPO, ZI, PVT, MDT (value-based choice selection) raphe pontis nucleus, contralateral LHb and REM-promoting PnO (Herkenham and Nauta, 1979; Araki et al., 1988). So I predict that LHb suppresses SWS-promoting LPO and IPN (LHb inhibition of MRN is well-known). I propose that LHb attenuates wake-on cholinergic, GABAergic or glutamatergic neurons in LDT, PPT, NBM/SI, MS/DBB, then noradrenergic LC, histaminergic PH/TMN, orexinergic LH, glutamatergic SUM, possibly also VTg, DTg, ZI, SC, PAG, CM and MDT to decrease movement and arousal in chronically hostile environment and during REM. Chronic pain and chronic negative feedback overstimulate LHb, causing learned helplessness, to stop us moving or exert/lose energy for things that repeatedly hurt and harm us. There is no need to suppress REM-on LDT or PPT groups by LHb in REM as they might be used to trigger the theta-frequency in SUM (PPT/LDT activate SubC and medullary reticular nuclei that inhibit motorneurons in REM, causing muscle atonia). Overstimulation of LHb, by loss, worries, bad outcomes, or by low basal dopamine or serotonin signal actually causes longer REM and less SWS. As was found in depression (Steriade and McCarley, 1990). This supports my prediction that LHb is one of effectors activated by REM-on system in PnO or SubC. Wake-on orexinergic LH neurons possibly inhibit LHb and RMTg, causing rise in VTA/SNc dopamine, while the REM-on MCH neurons of LH might inhibit dopaminergic A11 stimulation of motor neurons and activate SubC or PnO.
Predicted suppression of NBM by LHb (e.g. in depression, defeat) then decreases attention, WM and gamma based cortical coupling. As tonic, fast oscillatory (20–40 Hz) cortical activity is elicited by BNM stimulation (Metherate et al., 1992).

Reticular nucleus pontis oralis and caudalis, PnO and PnC

Nucleus pontis caudalis (PnC) and oralis (PnO/RPO) induce REM sleep. Both project to oculomotor/visual system. PnC projections to STN might enhance the REM linked motor response suppression. Movement suppression in REM is caused by SubC that inhibits motor spinal neurons via reticular medullar nuclei. Wake-on noradrenaline inhibits SubC and wake-on PPT group inhibits PnC. Theta inducing PnO projects to SUM, LDT, IPN, lateral mamillary body (LMB), mesencephalic reticular formation (that projects to reticular thalamic, reuniens and subthalamic nucleus), retrorubral nucleus, VTA, SNc, specific PAG regions, zona incerta (ZI) and CM (Vertes and Martin, 1998). So question is why the PnO interacts with the LMB in REM? The LMB connects with RSC, EC, DTg, postsubicular hippocampus and AD, and might enable a navigation on temporal axes (distant past, less distant past...) of memory, what is not a strong feature of dreams.

Theta oscillations are evoked either during active waking state by what is going on around us, so by contextual and stimulus based novelty, salient sensory input, interesting or meaningful stimuli, good/valuable or bad/harmful things; and also by REM-on PnO (maybe via LDT to MS). In quiet waking without novelty and during consumatory (repetitive) behaviour there is low need to record new information, so it might be linked to replay. Possibly when hippocampal dentate gyrus gets full and new information leads to interference, the hippocampus stimulates posterior septum to induce SWS via MHb-pathway, to clean up short term storage for new input. The MHB → IPN → MRN circuit then promotes SWS and antagonizes theta promoting circuit, wake and REM sleep.

REFERENCES

Aizawa H, Kobayashi M, Tanaka S, Fukai T, Okamoto H. Molecular characterization of the subnuclei in rat habenula. J Comp Neurol 2012; 520: 4051066. Abstract

Antolin-Fontes B, Ables JL, Gorlich A, Ibanez-Tallon I (2014). The habenulo-interpeduncular pathway in nicotine aversion and withdrawal. Neuropharmacology 96 (Pt B): 2132.

Araki M, McGeer PL, Kimura H (1988) The efferent projections of the rat lateral habenular nucleus revealed by the PHA-L anterograde tracing method. Brain Res, 44, 31930.

Aston-Jones G, Bloom FE (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci-1:876-886.

Axelrod J (1970). "The pineal gland". Endeavour 29 (108): 144.
Balcita-Pedicino J. J., Omelchenko N., Bell R., Sesack S. R. (2011). The inhibitory influence of the lateral habenula on midbrain dopamine cells: ultrastructural evidence for indirect mediation via the rostromedial mesopontine tegmental nucleus. J. Comp. Neurol. 519, 1143164 10.1002/cne.22561 [PMC free article] [PubMed]

Bernard, R., Lydic, R. & Baghdoyan, H. A. Hypocretin-1 activates G proteins in arousal-related brainstem nuclei of rat. Neuroreport 13, 44750 (2002). Article

Bittencourt JC, Sawchenko PE (2000) Do centrally administered neuropeptides access cognate receptors? An analysis in the central corticotropin-releasing factor system. J Neurosci, 20 (3),1142156.

Bland B. H., Oddie S. D. (2001). Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. Behav. Brain Res. 127, 11936. [PubMed]

Blumberg MS, Karlsson KA, Seelke AM, Mohns EJ. The ontogeny of mammalian sleep: a response to Frank and Heller (2003) J Sleep Res. 2005;14:918. [PMC free article].

Bogdanski DF, Weissbach H, Udenfriend S (1958) J. Pharmacol. Exp. Therap. 122, 182.

Brown R. E., McKenna J. T. (2015). Turning a negative into a positive: ascending GABAergic control of cortical activation and arousal. Front. Neurol. 6:135. PubMed

Buzsaki G. Two-stage model of memory trace formation: a role for ?oisybrain states. Neuroscience. 1989;31:55170. [PubMed]

Buzsaki G. Theta oscillations in the hippocampus. Neuron. 2002;33:32540. [PubMed]

Cespuglio R, Gomez ME, Faradji H, Jouvet M. Alterations in the sleep-waking cycle induced by cooling of the locus coeruleus area. Electroencephalogr Clin Neurophysiol. 1982;54:57078. [PubMed]

Christoph GR, Leonzio RJ, Wilcox KS (1986) Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. J Neurosci 6:613-619.

Claudio Cuello A, Emson PC, Paxinos G, Jessell T (1978). Substance P containing and cholinergic projections from the habenula. Brain Res. 149, 41329 10.1016/0006-8993(78)90484-5 [PubMed]

Contestabile A, Flumerfelt BA (1981) Afferent connections of the interpeduncular nucleus and the topographic organization of the habenulo-interpeduncular pathway: an HRP study in the rat. Comp Neurol, 196:25370.

Costa R, Pscheidt GR, van Meter WG, Himwich HE, J. Pharmacol. Exp. Therap. 130,81 (1960).
Dahan L, Astier B, Vautrelle N, Urbain N, Kocsis B, Chouvet G. Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. Neuropsychopharmacology. 2007 Jun;32(6):1232-41.

Datta S, Mavanji V, Patterson EH, Ulloor J. Regulation of rapid eye movement sleep in the freely moving rat: local microinjection of serotonin, norepinephrine, and adenosine into the brain stem. Sleep. 2003;26:51320. [PubMed]

Delorme F (1966) thesis, University of Lyons.

Dillingham CM, Holmes JD, Wright NF, Erichsen JT, Aggleton JP, Vann SD. Calcium-binding protein immunoreactivity in Gudden tegmental nuclei and the hippocampal formation: differential co-localization in neurons projecting to the mammillary bodies. Frontiers in Neuroanatomy. 2015;9:103.

Gervasoni D, Darracq L, Fort P, Souliere F, Chouvet G, Luppi PH (1998) Electrophysiological evidence that noradrenergic neurons of the rat locus coeruleus are tonically inhibited by GABA during sleep. Eur J Neurosci 10:96470. [PubMed]

Gervasoni D, Peyron C, Rampon C, Barbagli B, Chouvet G, Urbain N, Fort P, Luppi PH (2000) Role and origin of the GABAergic innervation of dorsal raphe serotonergic neurons. J Neurosci 20:4217225. [PubMed]

Goto M, Swanson LW, Canteras NS (2001) Connections of the nucleus incertus. J Comp Neurol438: 8622. Abstract Full Article (HTML)

Gottesfeld Z. (1983). Origin and distribution of noradrenergic innervation in the habenula: a neurochemical study. Brain Res. 275, 299-304. 10.1016/0006-8993(83)90990-3 [PubMed].

Greco MA, Shiromani PJ. Hypocretin receptor protein and mRNA expression in the dorsolateral pons of rats. Brain Res Mol Brain Res 2001; 88: 17682. PubMed

Groenewegen HJ, Ahlenius S, Haber SN, Kowall NV, Nauta WJ (1986) Cytoarchitecture, fiber connections, and some histochemical aspects of the interpeduncular nucleus in the rat. J. Comp Neurol, 249: 6502.

Guilding C, Piggins HD (2007) Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? Eur J Neurosci 25:3195216.

Hayakawa, T., Ito, H., Zyo, K., 1993. Neuroanatomical study of afferent projections to the supramammillary nucleus of the rat. Anat. Embryol. 188, 13948.

Herkenham M. (1981) Anesthetics and the habenulo-interpeduncular system: selective sparing of metabolic activity. Brain Res 210:46166.

Herkenham M, Nauta WJ (1977) Afferent connections of the habenular nuclei in the rat. A horseradish peroxidase study, with a note on the fiber-of-passage problem. J Comp Neurol 173:12345.

Herkenham M, Nauta WJ (1979) Efferent connections of the habenular nuclei in
the rat. J Comp Neurol 187:19-47.

Irle E, Sarter M, Guldin WO, Markowitsch HJ. Afferents to the ventral tegmental nucleus of Gudden in the mouse, rat, and cat. J Comp Neurol. 1984;228:50941. [PubMed]

Jacobs BL, Azmitia EC (1992) Structure and function of the brain serotonin system Physiol Rev 2:16529.

Jacobs BL, Henriksen SJ, Dement WC. Neurochemical bases of the PGO wave. Brain Res. 1972;48:40611. [PubMed]

James MD, MacKenzie EJ, Tuohy-Jones PA, Wilson CA (1987) Dopaminergic neurones in the zona incerta exert a stimulatory control on gonadotrophin release via D1 dopamine receptors. Neuroendocrinology, 45: 348 355.

Jhou, TC, Geisler, S, Marinelli, M, Degarmo, BA & Zahm, DS (2009) The mesopontine rostromedial tegmental nucleus: A structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. J.  Comp. Neurol. 513, 56696.

Jhou T, Fields HL, Baxter MG, Saper CB, Holland PC (2009) The Rostromedial Tegmental Nucleus (RMTg), a GABAergic Afferent to Midbrain Dopamine Neurons, Encodes Aversive Stimuli and Inhibits Motor Responses. Neuron, 61:5, 78600.

Ji H, Shepard PD (2007) Lateral Habenula Stimulation Inhibits Rat Midbrain Dopamine Neurons through a GABAA Receptor-Mediated Mechanism. J Neurosci, 27, 6923930.

Jouvet M. Recherches sur les structures nerveuses et les mecanismes responsables des differentes phases du sommeil physiologique. Arch Ital Biol. 1962;100:12506. [PubMed]

Jouvet M, Bobillier P, Pujol JF, Renault J (1967) Permanent insomnia and diminution of cerebral serotonin due to lesion of the raphe system in cats. J Physiol, 59:248. [PubMed]

Kaufling J, Veinante P, Pawlowski SA, Freund-Mercier MJ, Barrot M.(2009) Afferents to the GABAergic tail of the ventral tegmental area in the rat. J Comp Neurol. 513, 597-621.

Kilduff TS, Peyron C (2000) The hypocretin/orexin ligand receptor system: implications for sleep and sleep disorders. Trends Neurosci. 23, 35965 . Article

Kim U (2009) Topographic commissural and descending projections of the habenula in the rat. J Comp Neurol; 513: 17387. Abstract

Kim T, Thankachan S, McKenna JT, McNally JM, Yang C, Choi JH, et al. (2015) Cortically projecting basal forebrain parvalbumin neurons regulate cortical gamma band oscillations. Proc Natl Acad Sci U S A, 112(11):3535-3540. [PubMed]

Kim U, Chang S (2005) Dendritic morphology, local circuitry, and intrinsic electrophysiology of neurons in the rat medial and lateral habenular nuclei of the
epithalamus. J Comp Neurol 483: 23650.

Kinney GG, Kocsis B, Vertes RP. Injections of excitatory amino acid antagonists into the median raphe nucleus produce hippocampal theta rhythm in the urethane anesthetized rat. Brain Res. 1994;654:9604. [PubMed]

Kinney GG, Kocsis B, Vertes RP. Injections of muscimol into the median raphe nucleus produce hippocampal theta rhythm in the urethane anesthetized rat. Psychopharmacology. 1995;120:24448. [PubMed]

Kinney GG, Kocsis B, Vertes RP. Medial septal unit firing characteristics following injections of 8-OH-DPAT into the median raphe nucleus. Brain Res. 1996;708:11622. [PubMed]

Kiss J, Csaki A, Bokor H, Kocsis K, Kocsis B (2002) Possible glutamatergic/aspartatergic projections to the supramammillary nucleus and their origins in the rat studied by selective [(3)H]D-aspartate labelling and immunocytochemistry. Neuroscience 111:67191.

Lavezzi HN, Parsley KP, Zahm DS. 2014. Modulation of locomotor activation by the rostromedial tegmental nucleus. Neuropsychopharmacology 40:67687. [PubMed]

Lodge DJ, Grace AA (2006) The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. Proc Natl Acad Sci U S A. 2006 Mar 28; 103(13):5167-72. [PubMed]

Luebke JI, Greene RW, Semba K, Kamondi A, McCarley RW, Reiner PB. Serotonin hyperpolarizes cholinergic low-threshold burst neurons in the rat laterodorsal tegmental nucleus in vitro. Proc Natl Acad Sci USA. 1992;89:74347. [PMC free article]

Lydic R, Baghdoyan HA (2005) Sleep, anesthesiology, and the neurobiology of arousal state control. Anesthesiology. 2005 Dec; 103(6):1268-95. [PubMed]

Lydic R, McCarley RW, Hobson JA. The time-course of dorsal raphe discharge, PGO waves, and muscle tone averaged across multiple sleep cycles. Brain Res. 1983;274:36570. [PubMed]

Ma S, Olucha-Bordonau FE, Hossain MA, Lin F, Kuei C, Liu C, Wade JD, Sutton SW, Nunez A, Gundlach AL. Modulation of hippocampal theta oscillations and spatial memory by relaxin-3 neurons of the nucleus incertus. Learn Mem 2009; 16: 73042. [PubMed]

Mani BK, Walker AK, Lopez Soto EJ, Raingo J, Lee CE, Perello M, Andrews ZB, Zigman JM. Neuroanatomical characterization of a growth hormone secretagogue receptor-green fluorescent protein reporter mouse. J Comp Neurol 2014; 522: 3644666. [Abstract]

Maru E, Takahashi LK, Iwashara S (1979) Effects of median raphe nucleus lesions on hippocampal EEG in the freely moving rat. Brain Res,163 : 22334.
Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M, Elmquist JK. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol 2001; 435: 65. Abstract

Marrosu, F., Portas, C., Mascia, M. S., Casu, M. A., Fa, M., Giagheddu, M., et al. (1995). Microdialysis measurement of cortical and hippocampal acetylcholine release during sleep-wake cycle in freely moving cats. Brain Res. 671, 32932.

Marrosu F, Fornal CA, Metzler CW, Jacobs BL (1996) 5-HT 1A agonists induce hippocampal theta activity in freely moving cats: role of presynaptic 5-HT 1A receptors. Brain Res 739:19200.

Matsumoto, M; Hikosaka O (2007). Lateral habenula as a source of negative reward signals in dopamine neurons. Nature 447 (7148): 1111115.

McCormick DA., Prince DA (1987) Actions of acetylcholine in the guinea-pig and cat medial and lateral geniculate nuclei, in vitro. J Physiol 392:14765.

McGinty DJ, Harper RM (1976) Dorsal raphe neurons: depression of firing during sleep in cats. Brain Res 101:56975. CrossRef

Metherate R, Cox CL, Ashe JH (1992) Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. 12:4701-4711.

Miyamoto Y, Watanabe Y, Tanaka M. Developmental expression and serotonergic regulation of relaxin 3/INSL7 in the nucleus incertus of rat brain. Regul Pept 2008; 145: 549. PubMed

Monnier M and Tissot R, (1958) Helv. Physiol Pharmacol Acta 16, 255.

Oddie SD, Bland BH, Colom LV, Vertes RP (1994) The midline posterior hypothalamic region comprises a critical part of the ascending brainstem hippocampal synchronizing pathway. Hippocampus, 4, 45473. Abstract

O'Keefe J., Recce M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3, 31730. [PubMed]

Olucha-Bordonau FE, Teruel V, Barcia-Gonzalez J, Ruiz-Torner A, Valverde-Navarro AA, Martinez-Soriano F. Cytoarchitecture and efferent projections of the nucleus incertus of the rat. J Comp Neurol 2003; 464: 627. Abstract

Olucha-Bordonau FE, Otero-Garcia M, Sanchez-Perez AM, Nunez A, Ma S, Gundlach AL. Distribution and targets of the relaxin-3 innervation of the septal area in the rat. J Comp Neurol 2012; 520: 1903939. Abstract

Park MR (1987) Monosynaptic inhibitory postsynaptic potentials from lateral habenula recorded in dorsal raphe neurons. Brain Res Bull 19:581-586.

Perrotti LI, Bolanos CA, Choi KH, Russo SJ, Edwards S, Ulery PG, Wallace DL, Self DW, Nestler EJ, Barrot M (2005) DeltaFosB accumulates in a GABAergic cell population in the posterior tail of the ventral tegmental area after psychostimulant treatment. Eur J Neurosci 21:2817824. Abstract
Phillipson OT, Pycock CJ. 1982. Dopamine neurons of the ventral tegmentum project to both medial and lateral habenula. Exp Brain Res 45: 894.

Qin C and Luo M. (2009). Neurochemical phenotypes of the afferent and efferent projections of the mouse medial habenula. Neuroscience 161:82737.

Quick MW, Ceballo RM, Kasten M, McIntosh JM, Lester RA (1999) α3β 4 subunit-containing nicotinic receptors dominate function in rat medial habenula neurons. Neuropharmacology 38:76983.

Raisman G (1966) The connections of the septum. Brain 89: 317-348.

Ren J, Qin C, Hu F, Tan J, Qiu L, Zhao S, Feng G, Luo M (2011). Habenula holinergic neurons co-release glutamate and acetylcholine and activate postsynaptic neurons via distinct transmission modes. 69:44552.

Reuss S, Moller M. 1986. Direct projections to the rat pineal gland via the stria medullaris thalami. Cell Tissue Res 244: 69194. PubMed

Ronnekleiv OK, Kelly MJ, Wuttke W. Single unit recordings in the rat pineal gland: evidence for habenulo-pineal neural connections. Exp Brain Res 39: 18792, 1980 PubMed

Ronnekleiv OK, Moller M. Brain-pineal nervous connections in the rat: an ultrastructure study following habenular lesion. Exp. Brain Res. 1979;37:55162. PubMed

Roffwarg HP, Muzio JN, Dement WC (1966) Ontogenetic development of the human sleep-dream cycle Science 29; 152(3722):604-19. PubMed

Saito Y, Cheng M, Leslie FM, Civelli O. Expression of the melanin-concentrating hormone (MCH) receptor mRNA in the rat brain. J Comp Neurol 2001; 435: 260. Abstract

Sakai K. (1980). “Some anatomical and physiological properties of pontomesencephalic tegmental neurons with special reference to PGO waves and postural atonia during paradoxical sleep,” in The Reticular Formation Revisited, eds Hobson J. A., Brazier M. A. B., editors. (New York: Raven Press; ), 427–447.

Sakurai T. (2007). The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat. Rev. Neurosci. 8, 17181 10.1038/nrn2092 PubMed

Sanchez-Perez, A. M., Arnal-Vicente, I., Santos, F. N., Pereira, C. W., ElMili, N., Sanjuan, J., et al. (2015). Septal projections to nucleus incertus in the rat: bidirectional pathways for modulation of hippocampal function. J. Comp. Neurol. 523, 56588.

Saper, C. B., Chou, T. C. & Scammell, T. E. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24, 72631 (2001). PubMed Article

Steininger, T. L., Gong, H., McGinty, D. & Szmusiak, R. Subregional organization of preoptic area/anterior hypothalamic projections to arousal-related monoaminergic cell groups. J. Comp. Neurol. 429, 63853 (2001). Article
Strecker, R. E. et al. Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav. Brain Res. 115, 18304 (2000). Article

Sutherland RJ (1982) The dorsal diencephalic conduction system: a review of the anatomy and functions of the habenular complex. Neurosci Biobehav Rev 6:13.

Sugama S., Cho B. P., Baker H., Joh T. H., Lucero J., Conti B. (2002). Neurons of the superior nucleus of the medial habenula and ependymal cells express IL-18 in rat CNS. Brain Res. 958, 1 10.1016/S0006-8993(02)03363-2 [PubMed]

Takahashi, K., Kayama, Y., Lin, J. S., and Sakai, K. (2010). Locus coeruleus neuronal activity during the sleep-waking cycle in mice. Neuroscience 169, 1115126.

Takahashi K., Lin J.S., Sakai K. Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. J.Neurosci. 2006;26:102920298. [PubMed]

Teclemariam-Mesbah, R., Ter Horst, G. J., Fostema, F., Wotel, J. & Buijs, R. M. Anatomical demonstration of the suprachiasmatic nucleus-pineal gland. J. Comp. Neurol. 406, 17182 (1999). Article

Teruel-Marti V, Cervera-Ferri A, Nunez A, Valverde-Navarro AA, Olucha-Bordonau FE, Ruiz-Torner A. Anatomical evidence for a ponto-septal pathway via the nucleus incertus in the rat. Brain Res 2008; 1218: 876. PubMed

Thakkar MM, Strecker RE, McCarley RW. Behavioral state control through differential serotonergic inhibition in the mesopontine cholinergic nuclei: a simultaneous unit recording and microdialysis study. J Neurosci. 1998;18:5490497. [PMC free article]

Thinschmidt, J.S., 1993. The supramammillary nucleus: does it play a role in the mediation of hippocampal theta rhythm? MA Thesis. Florida Atlantic University.

Trulson ME, Jacobs BL (1979) Raphe unit activity in freely moving cats: correlation with level of behavioral arousal. Brain Res 163:13550.

Uhlhaas PJ, Roux F, Singer W, Haenschel C, Sireteanu R, Rodriguez E (2009) The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. Proc Natl Acad Sci USA;106:9866871. [PMC free article]

Vaccari C, Lolait SJ, Ostrowski NL. Comparative distribution of vasopressin V1b and oxytocin receptor messenger ribonucleic acids in brain. Endocrinology 1998; 139: 5015033. PubMed

VadovičovK. (2014) Affective and cognitive prefrontal cortex projections to the lateral habenula in humans. in Front Hum Neurosci. 2014; 8:819. Also published in arXiv:1402.2196 [q-bio.NC]

Vadovičov K., Gasparotti, R. (2014). Reward and adversity processing circuits: their competition and interactions with dopamine and serotonin signaling.
Vanderwolf, C.H. (1969) Hippocampal electrical activity and voluntary movement in the rat. Electroencephalogr. Clin. Neurophysiol., 26, 40718. PubMed

Varga V, Kekesi A, Juhasz G, Kocsis B (1998) Reduction of the extracellular level of glutamate in the median raphe nucleus associated with hippocampal theta activity in the anaesthetized rat. Neuroscience. 1998 May;84(1):49-57

Vertes RP and Fass B (1988) Projections between the interpeduncular nucleus and basal forebrain in the rat as demonstrated by the anterograde and retrograde transport of WGA-HRP. Exp. Brain Res., 73: 231.

Vertes RP, Kinney GG, Kocsis B, Fortin WJ (1994) Pharmacological suppression of the median raphe nucleus with serotonin1A agonists, 8-OH-DPAT and buspirone, produces hippocampal theta rhythm in the rat. Neuroscience, 60:44151. PubMed

Vertes, R.P. & Kocsis, B. (1997) Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. Neuroscience, 81, 89326. PubMed

Vertes RP, Linley SB (2008) in Serotonin and sleep: molecular, functional and clinical aspects, Efferent and afferent connections of the dorsal and median raphe nuclei in the rat, eds Monti JM, Pandi-Perumal SR, Jacobs BL, Nutt DJ (Birkh?ser Verlag, Basel), pp 6902. Google Scholar

Vertes, R. P. and Martin, G. F. (1988), Autoradiographic analysis of ascending projections from the pontine and mesencephalic reticular formation and the median raphe nucleus in the rat. J. Comp. Neurol., 275: 51141. doi:10.1002/cne.902750404

Wang RY, Aghajanian GK (1977) Physiological evidence for habenula as major link between forebrain and midbrain raphe. Science 197:89-91.

Wasserman DI, Wang HG, Rashid AJ, Josselyn SA, Yeomans JS. 2013. Cholinergic control of morphine-induced locomotion in rostromedial tegmental nucleus versus ventral tegmental area sites. Eur J Neurosci 38:2774785. Abstract

Wasserman DI, Tan JMJ, Kim J, Yeomans JS. 2014. Muscarinic control of rostromedial tegmental nucleus (RMTg) GABA neurons and morphine-induced locomotion. Soc Neurosci Abstr 364.02.

Williams JA, Comisarow J, Day J, Fibiger HC, Reiner PB (1994) State-dependent release of acetylcholine in rat thalamus measured by in vivo microdialysis. 14:5236242. Abstract

Williams JA, Reiner PB. Noradrenaline hyperpolarizes identified rat mesopontine cholinergic neurons in vitro. J Neurosci. 1993;13:3878883. [PubMed]

Woolf NJ (1991) Cholinergic systems in mammalian brain and spinal cord. Progress in Neurobiology, 37, 475-524.
Yamaguchi T., Danjo T., Pastan I., Hikida T., Nakanishi S. (2013). Distinct roles of segregated transmission of the septo-habenular pathway in anxiety and fear. Neuron. 78, 5374-5384. 10.1016/j.neuron [PMC free article] [PubMed]

Yamamoto T, Watanabe S, Oishi R, Ueki S (1979) Effects of midbrain raphe stimulation and lesion on EEG activity in rats. Brain Res Bull, 4:491-495.

Yoon JY, Jung SR, Hille B, Koh DS (2014) Modulation of nicotinic receptor channels by adrenergic stimulation in rat pinealocytes. Am J Physiol Cell Physiol; 306:C726-C735.  View Article

Zahm DS. 2006. The evolving theory of basal forebrain functional-anatomical and acrosystems. Neurosci Biobehav Rev 30:1487-2. PubMed

Zahm DS, Jensen SL, Williams ES, Martin JR 3rd. 1999. Direct comparison of projections from the central amygdaloid region and nucleus accumbens shell. Eur J Neurosci 11:1119-126. Abstract Full Article (HTML)

Zahm DS, Parsley KP, Schwartz ZM, Cheng AY. 2013. On lateral septum-like characteristics of outputs from the accumbal hedonic hotspot of Pecina and Berridge with commentary on the transitional nature of basal forebrain boundaries. J Comp Neurol 521:508. Abstract Full Article (HTML)