The neural basis of the complex mental task of meditation: neurotransmitter and neurochemical considerations

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Summary   Meditation is a complex mental process involving changes in cognition, sensory perception, affect, hormones, and autonomic activity. Meditation has also become widely used in psychological and medical practices for stress management as well as a variety of physical and mental disorders. However, until now, there has been limited understanding of the overall biological mechanism of these practices in terms of the effects in both the brain and body. We have previously described a rudimentary neuropsychological model to explain the brain mechanisms underlying meditative experiences. This paper provides a substantial development by integrating neurotransmitter systems and the results of recent brain imaging advances into the model. The following is a review and synthesis of the current literature regarding the various neurophysiological mechanisms and neurochemical substrates that underlie the complex processes of meditation. It is hoped that this model will provide hypotheses for future biological and clinical studies of meditation.
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INTRODUCTION

The complex mental task of meditation is potentially one of the most important areas of research that may be pursued by science in the next decade. Meditation offers a fascinating window into human consciousness, psychology, and experience; the relationship between mental states and body physiology; emotional and cognitive processing; and the biological correlates of religious experience. In the past thirty years, scientists have explored the biological effects and mechanisms of meditation in great detail. Initial studies measured changes in autonomic activity such as heart rate and blood pressure, as well as electroencephalographic (EEG) changes. More

recent studies have explored changes in hormonal and immunological function associated with meditation. Studies have also explored the clinical effects of meditation in both physical and psychological disorders.

Functional neuroimaging has opened a new window into the investigation of meditative states by exploring the neurological correlates of these experiences. Five studies, currently available in the literature (see Table 1), measured cerebral function during meditation techniques. These neuroimaging techniques include positron emission tomography [PET; (1–3)], single photon emission computed tomography [SPECT; (4)], and functional magnetic resonance imaging [fMRI; (5)]. Each of these techniques provides different advantages and disadvantages in the study of meditation. Although functional MRI has the ability of immediate anatomic correlation and has improved resolution over SPECT, it would be very difficult to utilize for the study of meditation because of the noise from the machine and the problem of requiring the subject to lie prone in the machine, an atypical posture for many forms of meditation. In fact, we attempted the use of

Table 1 Summary of current neuroimaging studies of meditation

Study	Type of meditation	Imaging modality	N^a	Measures	Results	Critique
Herzog et al. (1)	Yoga	PET	8	CBF	↑Frontal lobe, ↓parietal lobe	Meditation in the scanner, limited regional analysis, one time point
Lou et al. (2)	Tantric Yoga	PET	9	CBF	↑Parietal during focus on self, ↑hippocampus, ↓PFC	Subjects listened to tape guiding the meditation, different forms of meditation, one time point
Newberg et al. (4)	Tibetan	SPECT	8	CBF	↑PFC, thalamus, brainstem, ↓PSPL	No cross correlation with other modalities, SPECT offers lowest resolution, one time point
Lazar et al. (5)	Kundalini	MRI	5	CBF	↑PFC, parietal, hippocampus, temporal lobe cingulate gyrus, hypothalamus	Attempted to factor in MRI noise to prevent distraction, smallest *N*, limited ability to detect decreased CBF, multiple time points
Kjaer et al. (3)	Yoga Nidra	PET	5	Dopamine	↑Dopamine in the striatum	Subjects listened to tape guiding the meditation, one time point, first neurotransmitter study

[a] *N* = number of subjects.

fMRI with one of our initial meditation subjects in order to determine feasibility, but the subject found it extremely difficult to carry out the meditation practice. While PET imaging also provides better resolution than SPECT, if one strives to make the environment relatively distraction free to maximize the chances of having a strong meditative experience, then it is sometimes beneficial to perform these studies during non-clinical times, which may make PET radiopharmaceuticals such as fluorodeoxyglucose difficult to obtain. Finally, the functional imaging techniques of PET and SPECT offer the opportunity to study changes in a variety of neurotransmitter systems in the brain associated with meditation practices. Overall, functional brain imaging offers important techniques for studying meditation, although the best approach may depend on factors related to each technique as well as specific parameters to be measured.

In this paper, we review existing data on the neurophysiology and physiology of meditation practices, and we attempt to integrate this data into a comprehensive neurochemical model of such practices. However, there are many possible neurochemical changes that may occur during meditation, even though they may not occur in every type of practice or in each individual. This model is designed to provide a framework of the neurological and physiological correlates of meditative experiences, and to create a springboard for future research.

TYPES OF MEDITATION

Although there are many specific approaches to meditation, we have typically divided such practices into two basic categories. The first category is one in which the subjects simply attempt to clear all thought from their sphere of attention. This form of meditation is one in which the practitioner attempts to reach a subjective state characterized by a sense of no space, no time, and no thought. Further, this state is cognitively experienced as fully integrated and unified, such that there is no sense of a self and other. This includes practices such as those associated with traditions such as Theravada Buddhism (6). The second category is one in which the subjects focus their attention on a particular object, image, phrase, or word, and it includes practices such as transcendental meditation and various forms of Tibetan Buddhism. This form of meditation is designed to lead one to a subjective experience of absorption with the object of focus. There is another distinction in which some meditation is guided by following along with a leader, either in person or on tape, who is verbally directing the practitioner. Others practice the meditation on their own volition. We might expect that this difference between volitional and guided meditation should also be reflected in specific differences in cerebral activation.

Phenomenological analysis suggests that the end results of many practices of meditation are similar, although these results might be described using different characteristics depending on the culture and individual. Therefore, it seems reasonable that while the initial neurophysiological activation occurring during any given practice may differ, there should eventually be a convergence. We present a description of volitional meditation, which will hopefully provide an overall framework from which any given type of meditation can be considered (see Fig. 1).
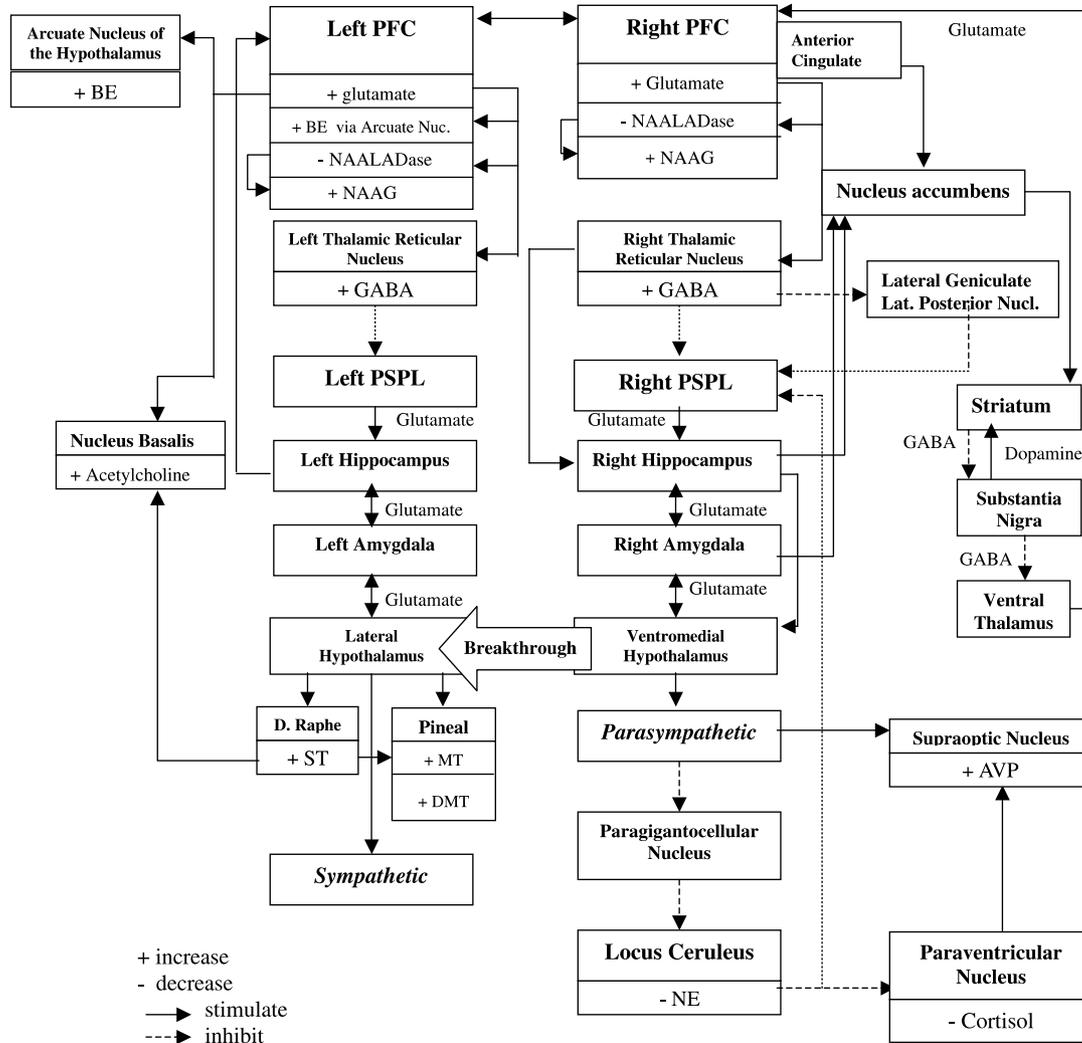
Fig. 1 Schematic overview of the neurophysiological network possibly associated with meditative states. The circuits and activations generally apply to both hemispheres even though they may be ascribed to only one hemisphere on the diagram below.

ACTIVATION OF THE PREFRONTAL AND CINGULATE CORTEX

Brain imaging studies suggest that willful acts and tasks that require sustained attention are initiated via activity in the prefrontal cortex (PFC), particularly in the right hemisphere (7–10). The cingulate gyrus appears to be involved in focusing attention, probably in conjunction with the PFC (11). Since meditation requires intense focus of attention, it seems appropriate that a model for meditation begin with activation of the PFC, particularly in the right hemisphere, as well as the cingulate gyrus. This notion is supported by the increased activity observed in these regions on several of the brain imaging studies of volitional types of meditation, including those from our laboratory (1,4,5). In our study of eight Tibetan Buddhist meditators, subjects had an intravenous line

placed in the arm, and were injected with a cerebral blood flow tracer while at rest in order to acquire a 'baseline' image. They then meditated for approximately 1 h when they were again injected with the tracer while they continued to meditate. At the time of injection, the tracer was fixed in the brain so that when the images were acquired approximately 20 min later, they reflected the cerebral blood flow during the meditation state. Quantitative analysis demonstrated increased activity in the PFC bilaterally (greater on the right) and the cingulate gyrus during meditation. Therefore, meditation appears to begin by activating the prefrontal and cingulate cortex associated with the will or intent to clear one's mind of thoughts or to focus on an object. One PET study of a guided type of meditation did not demonstrate increased prefrontal activity. However, a recent

study showed decreased frontal activity during externally guided word generation compared to internal or volitional word generation (12). Thus, prefrontal and cingulate activation may be associated with the volitional aspects of meditation.

THALAMIC ACTIVATION

Several animal studies have shown that the PFC, when activated, innervates the reticular nucleus of the thalamus (13), particularly as part of a more global attentional network (14). Such activation may be accomplished by the PFC's production and distribution of the excitatory neurotransmitter glutamate, which the PFC neurons use to communicate among themselves and to innervate other brain structures (15). The thalamus itself governs the flow of sensory information to cortical processing areas via its interactions with the lateral geniculate and lateral posterior nuclei and also likely uses the glutamate system in order to activate neurons in other structures (16). The lateral geniculate nucleus receives raw visual data from the optic tract and routes it to the striate cortex for processing (17). The lateral posterior nucleus of the thalamus provides the posterior superior parietal lobule (PSPL) with the sensory information it needs to determine the body's spatial orientation (18).

When excited, the reticular nucleus secretes the inhibitory neurotransmitter γ-aminobutyric acid (GABA) onto the lateral posterior and geniculate nuclei, cutting off input to the PSPL and visual centers in proportion to the reticular activation (19). During meditation, due to the increased activity in the PFC, particularly in the right hemisphere, there should be a concomitant increase in the activity in the reticular nucleus of the thalamus. While brain imaging studies of meditation have not yet had the resolution to distinguish the reticular nuclei, our recent SPECT study did demonstrate a general increase in thalamic activity that was proportional to the activity levels in the PFC. This finding is consistent with, but does not confirm, the specific interaction between the PFC and the reticular nuclei. If the activation of the right PFC causes activity to increase in the reticular nucleus during meditation, the result may be a decrease in sensory input entering into the PSPL. Several studies have demonstrated an increase in serum GABA during meditation (see Table 2 for an overview of neurochemical changes during meditation), possibly reflecting increased central GABA activity (20). This functional de-afferentation related to increased GABA would mean that fewer distracting outside stimuli would arrive at the visual cortex and PSPL enhancing the sense of focus.

It should also be noted that the dopaminergic system, via the basal ganglia, is believed to participate in regulating the glutamatergic system and the interactions between the prefrontal cortex and subcortical structures. A recent PET study utilizing 11C-Raclopride to measure the dopaminergic tone during Yoga Nidra meditation demonstrated a significant increase in dopamine levels during the meditation practice (3). The experimenters hypothesized that this increase may be associated with the gating of cortical–subcortical interactions, leading to an overall decrease in readiness for action that is associated with this particular type of meditation. Future studies will be necessary to elaborate on the role of dopamine during meditative practices, as well as on the interactions between dopamine and other neurotransmitter systems.

PSPL DEAFFERENTATION

The PSPL is heavily involved in the analysis and integration of higher-order visual, auditory, and somaesthetic information (21). It is also involved in a complex attentional network that includes the PFC and thalamus (22). Through the reception of auditory and visual input from the thalamus, the PSPL is able to help generate a three-dimensional image of the body in space, provide a sense of spatial coordinates in which the body is oriented, help distinguish between objects, and exert influences in regard to objects that may be directly grasped and manipulated (23,24). These functions of the PSPL may be critical for distinguishing between the self and the external world. It should be noted that a recent study has suggested that the superior temporal lobe may play a more important role than the parietal lobe in body spatial representation, although this has not been confirmed by

Table 2 Neurochemically related changes in serum concentration observed during meditation techniques and the central nervous system structures typically involved in their production

Neurochemical	Observed change	CNS structure
Arginine vasopressin	Increased (48)	Supraoptic nucleus
GABA	Increased (20)	Thalamus, other inhibitory structures
Melatonin	Increased (74)	Pineal gland
Serotonin	Increased (38)	Dorsal raphe
Cortisol	Decreased (38,43)	Paraventricular nucleus
Norepinephrine	Decreased (38,39)	Locus ceruleus
β-Endorphin	Rhythm changed; levels unaltered (52)	Arcuate nucleus

other reports (25). However, the actual relationship between the parietal and temporal lobes, in terms of spatial representation, remains to be fully elucidated.

Regardless, we propose that deafferentation of these orienting areas of the brain is an important concept in the physiology of meditation. If, for example, deafferentation of the PSPL via the reticular nucleus's GABA-ergic occurs, an individual may begin to lose his or her usual ability to spatially define the self and help to orient the self. Such a notion is supported by clinical findings in patients with parietal lobe damage who have difficulty orienting themselves. The effects of meditation are likely to be more selective, and instead of destroying the sense of self, they alter the perception of the self. Deafferentation of the PSPL has also been supported by two imaging studies demonstrating decreased activity in this region during intense meditation (1,4). Further, our SPECT study showed a significant correlation between increasing activity in the thalamus and decreasing activity in the PSPL.

HIPPOCAMPAL AND AMYGDALAR ACTIVATION

In addition to the complex cortical–thalamic activity, meditation might also be expected to alter activity in the limbic system, especially since stimulation of limbic structures is associated with experiences similar to those described during meditation (26,27). The hippocampus acts to modulate and moderate cortical arousal and responsiveness via rich and extensive interconnections with the prefrontal cortex, other neocortical areas, the amygdala, and the hypothalamus (28). Hippocampal stimulation has been shown to diminish cortical responsiveness and arousal; however, if cortical arousal is initially at a low level, then hippocampal stimulation tends to augment cortical activity (29). The ability of the hippocampus to stimulate or inhibit neuronal activity in other structures likely relies upon the glutamate and GABA systems, respectively (16). The partial deafferentation of the right PSPL during meditation may result in stimulation of the right hippocampus because of the inverse modulation of the hippocampus in relation to cortical activity. If, in addition, there is simultaneous direct stimulation of the right hippocampus via the thalamus (as part of the known attentional network) and mediated by glutamate, then a powerful recruitment of stimulation of the right hippocampus occurs. Right hippocampal activity may ultimately enhance the stimulatory function of the PFC on the thalamus via the nucleus accumbens, which gates the neural input from the PFC to the thalamus via the neuromodulatory effects of dopamine (30,31).

The hippocampus greatly influences the amygdala, such that they complement and interact in the genera-

tion of attention, emotion, and certain types of imagery (28). It seems as though much of the prefrontal modulation of emotion is via the hippocampus and its connections with the amygdala (32). Because of this reciprocal interaction between the amygdala and hippocampus, the activation of the right hippocampus likely stimulates the right lateral amygdala as well. The results of the fMRI study by Lazar et al. (5) support this notion of increased activity in the regions of the amygdala and hippocampus during meditation.

HYPOTHALAMIC AND AUTONOMIC NERVOUS SYSTEM CHANGES

The hypothalamus is extensively interconnected with the limbic system. Stimulation of the right lateral amygdala has been shown to result in stimulation of the ventromedial portion of the hypothalamus with a subsequent stimulation of the peripheral parasympathetic system (33). Increased parasympathetic activity should be associated with the subjective sensation first of relaxation and, eventually, of a more profound quiescence. Activation of the parasympathetic system would also cause a reduction in heart rate and respiratory rate. All of these physiological responses have been observed during meditation (34).

Typically, when an individual's breathing and heart rate slow down, the paragigantocellular nucleus of the medulla ceases to innervate the locus ceruleus (LC) of the pons. The LC produces and distributes norepinephrine (NE) (35). NE is a neuromodulator that increases the susceptibility of brain regions to sensory input by amplifying strong stimuli, while simultaneously gating out weaker activations and cellular 'noise' that fall below the activation threshold (36). Decreased stimulation of the LC results in a decrease in the level of NE (37). The breakdown products of catecholamines such as NE and epinephrine have generally been found to be reduced in the urine and plasma during meditation (38,39). Although this may simply reflect the systemic change in autonomic balance, the changes are not inconsistent with a cerebral decrease in NE levels as well. During a meditative practice, the reduced firing of the paragigantocellular nucleus probably cuts back its innervation of the locus ceruleus, which densely and specifically supplies the PSPL and the lateral posterior nucleus with NE (35). Thus, a reduction in NE would decrease the impact of sensory input on the PSPL, contributing to its deafferentation.

The locus ceruleus would also deliver less NE to the hypothalamic paraventricular nucleus. The paraventricular nucleus of the hypothalamus typically secretes corticotropin-releasing hormone (CRH) in response to innervation by NE from the locus ceruleus (40). This

CRH stimulates the anterior pituitary to release adreno-corticotropic hormone (ACTH) (41). ACTH, in turn, stimulates the adrenal cortex to produce cortisol, one of the body's stress hormones (42). Decreasing NE from the locus ceruleus during meditation would likely decrease the production of CRH by the paraventricular nucleus, which would ultimately decrease cortisol levels. Most studies have found that urine and plasma cortisol levels are decreased during meditation (38,43,44).

The drop in blood pressure associated with parasympathetic activity during meditation practices would be expected to relax the arterial baroreceptors leading the caudal ventral medulla to decrease its GABAergic inhibition of the supraoptic nucleus of the hypothalamus. This lack of inhibition can provoke the supraoptic nucleus to release the vasoconstrictor arginine vasopressin (AVP), thereby tightening the arteries and returning blood pressure to its normal level (45). AVP has also been shown to contribute to the general maintenance of positive affect (46), to decrease self-perceived fatigue and arousal, and to significantly improve the consolidation of new memories and learning (47). In fact, plasma AVP has been shown to increase dramatically during meditation (48). The sharp increase in AVP should result in a decreased subjective feeling of fatigue and an increased sense of arousal. It could also help to enhance the meditator's memory of his experience, perhaps explaining the subjective phenomenon that meditative experiences are remembered and described in very vivid terms.

PFC EFFECTS ON OTHER NEUROCHEMICAL SYSTEMS

As a meditation practice continues, there should be continued activity in the PFC associated with the individual's persistent will to focus attention. In general, as PFC activity increases, it produces ever-increasing levels of free synaptic glutamate in the brain. Increased glutamate can stimulate the hypothalamic arcuate nucleus to release β-endorphin (49). β-endorphin (BE) is an opioid produced primarily by the arcuate nucleus of the medial hypothalamus and distributed to the brain's subcortical areas (50). BE is known to depress respiration, reduce fear, reduce pain, and produce sensations of joy and euphoria (51). That such effects have been described during meditation may implicate some degree of BE release related to the increased PFC activity. Meditation has been found to disrupt diurnal rhythms of BE and ACTH (52). However, it is likely that BE is not the sole mediator in such experiences during meditation because simply taking morphine-related substances does not produce equivalent experiences as in meditation and one very limited study demonstrated that blocking the

opiate receptors with naloxone did not affect the experience or EEG associated with meditation (53).

Glutamate activates *N*-methyl-D-aspartate receptors (NMDAr), but excess glutamate can kill these neurons through excitotoxic processes (54). We propose that if glutamate levels approach excitotoxic concentrations during intense states of meditation, the brain might limit its production of N-acetylated-α-linked-acidic dipeptidase, the enzyme responsible for converting the endogenous NMDAr antagonist *N*-acetylaspartylglutamate (NAAG) into glutamate (55). The resultant increase in NAAG would protect cells from excitotoxic damage. There is an important side effect, however, since the NMDAr inhibitor, NAAG, is functionally analogous to the disassociative hallucinogens ketamine, phencyclidine, and nitrous oxide (56). These NMDAr antagonists produce a variety of states that may be characterized as either schizophrenomimetic or mystical, such as out-of-body and near-death experiences (57).

AUTONOMIC-CORTICAL ACTIVITY

In the early 1970s, Gellhorn and Kiely developed a model, based almost exclusively on autonomic nervous system (ANS) activity, of the physiological processes involved in meditation. Although the model was somewhat limited, it indicated the importance of the ANS during such experiences (58). These authors suggested that intense stimulation of either the sympathetic or parasympathetic system, if continued, could ultimately result in simultaneous discharge of both systems (what might be considered a 'breakthrough' of the other system). Several studies have demonstrated predominant parasympathetic activity during meditation associated with decreased heart rate and blood pressure, decreased respiratory rate, and decreased oxygen metabolism (34,43,59). However, a recent study of two separate meditative techniques suggested a mutual activation of parasympathetic and sympathetic systems by demonstrating an increase in the variability of heart rate during meditation (60). The increased variation in heart rate was hypothesized to reflect activation of both arms of the autonomic nervous system. This notion is consistent with recent developments in the study of autonomic interactions (61) and also fits the characteristic description of meditative states in which there is a sense of overwhelming calmness as well as significant alertness.

It should be noted that based upon current data, it is not clear if one hemisphere would exclusively initiate the neurological sequence of events over the other. This model presents the activity beginning in the right hemisphere, although other practices may activate the left first and some may be bilateral. Furthermore, it may be that the breakthrough of activity in the autonomic

nervous system may help with the stimulation of brain structures in both hemispheres. The other point about the model as presented is that all of the changes could occur in both hemispheres even though some events are associated with only one of the hemispheres in the model presented.

OTHER NEUROTRANSMITTER ACTIVITY

Activation of the autonomic nervous system can result in intense stimulation of structures in the lateral hypothalamus and median forebrain bundle, which are known to produce both ecstatic and blissful feelings when directly stimulated (62). Stimulation of the lateral hypothalamus can also result in changes in serotonergic activity. In fact, several studies have shown that after meditation, the breakdown products of serotonin (5-HT) in urine are significantly increased, suggesting an overall elevation in (5-HT) during meditation (38). Serotonin is a neuromodulator that densely supplies the visual centers of the temporal lobe. Within the temporal lobe, it strongly influences the flow of visual associations generated by this area (35). The cells of the dorsal raphe produce and distribute 5-HT when innervated by the lateral hypothalamus (63) and also when activated by the prefrontal cortex (64). Moderately increased levels of 5-HT appear to correlate with positive affect, while low 5-HT often signifies depression (65). This relationship has clearly been demonstrated with regards to the effects of the selective serotonin reuptake inhibitor medications which are widely used for the treatment of depression. When cortical $5-HT_2$ receptors (especially in the temporal lobes) are activated, however, the stimulation can result in a hallucinogenic effect. Tryptamine psychedelics such as psylocybin and LSD seem to take advantage of this mechanism to produce their extraordinary visual experiences (66). These visual hallucinations seem to occur because 5-HT inhibits the lateral geniculate nucleus, greatly reducing the amount of visual information that can pass through (67,68). If combined with reticular nucleus inhibition of the lateral geniculate, 5-HT may increase the fluidity of temporal visual associations in the absence of sensory input, possibly resulting in internally generated imagery that has been described during certain meditative states.

Increased 5-HT levels can affect several other neurochemical systems. An increase in serotonin has an effect on dopamine suggesting a link between the serotonergic and dopaminergic systems that may enhance the feelings of euphoria (69) that are frequently described during meditative states. Serotonin, in conjunction with the increased glutamate, has been shown to stimulate the nucleus basalis to release acetylcholine (ACh). ACh has important modulatory influences throughout the cortex

(70,71). For example, increased acetylcholine in the frontal lobes has been shown to augment the attentional system, and in the parietal lobes it tends to enhance orienting without altering sensory input (22). While no studies have evaluated the role of acetylcholine in meditation, it appears that this neurotransmitter may enhance the attentional component as well as the orienting response in the face of progressive deafferentation of sensory input into the parietal lobes during meditation. Increased serotonin, combined with lateral hypothalamic innervation of the pineal gland, may lead the latter to increase production of the neurohormone melatonin (MT) from the conversion of 5-HT (72). Melatonin has been shown to depress the central nervous system and reduce pain sensitivity (73). During meditation, blood plasma MT has been found to increase sharply (74), which may contribute to the feelings of calmness and decreased awareness of pain (75). Under circumstances of heightened activation, pineal enzymes can also endogenously synthesize the powerful hallucinogen 5-methoxy-dimethyltryptamine (DMT) (76). Several studies have linked DMT to a variety of mystical states, including out-of-body experiences, distortion of time and space, and interaction with supernatural entities (77,78). Hyperstimulation of the pineal at this step, then, could also lead to DMT production that could be associated with the wide variety of mystical-type experiences associated with that hallucinogen.

CONCLUSION

More avenues still need to be explored to better elucidate the intricate mechanisms underlying meditative practices. Most currently available studies of the biological correlates of meditation suffer from a low number of subjects, lack of control conditions, and difficulty in factoring out confounding variables. Furthermore, knowledge of neurotransmitter systems is highly complex and continually being refined. Thus, it may be very difficult to assess if all of the brain structures and neurotransmitter systems function in an integrated manner such as suggested in this paper. However, the neurophysiological effects that have been observed during meditative states seem to outline a consistent pattern of changes involving certain key cerebral structures in conjunction with autonomic and hormonal changes. These changes are also reflected in neurochemical changes involving the endogenous opioid, GABA, norepinephrine, and serotonergic receptor systems. The model presented here, based on current literature about the interaction of these systems, as well as brain imaging studies of meditative techniques, is an integrated hypothesis that may help to elucidate the mechanism underlying the physical and psychological effects of such

practices, and provide an impetus for future studies of these and other complex mental tasks.

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