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Contribution to Serotonin Theory of Dreaming (LSD Infusion)*

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THE CONSISTENCY AND MAGNITUDE *of the decrease of the latency of REM (rapid eye movement) and dream incidence by LSD (lysergic acid diethylamide) infusion warrant the assumption of a relationship between intracellular LSD increase (LSD has been shown to induce a serotonin-like reaction from human brain), and REM or dream incidence. A psychophysiologic mechanism capable of inducing dreams and hallucinations is described. It is concluded that paradoxical sleep is the physiologic manifestation of the interplay of a norepinephrine-dependent process fostering arousal and a serotonin-dependent process promoting sleep.*

SOME OF THE PSYCHOPHYSIOLOGIC factors responsible for sleep, paradoxical REM (rapid eye movement) sleep, and dreaming have been identified.[1-8] Animal experiments offer conclusive evidence that the prerequisite for falling asleep is a release of intracerebral serotonin.[2-4] Observations based mainly on the effects of intracerebral injections on the behavior and the electroencephalogram of animals led to the conclusion that paradoxical sleep is the physiologic manifestation of the interplay of two, at times opposing processes, namely, a norepinephrine-dependent process fostering arousal and a serotonin-dependent process promoting sleep.[4,6] Since dreaming and REM may also occur independently,[1] the conclusive experimental evidence based on animal studies regarding the processes underlying REM induction cannot be directly applied to dreams. Furthermore, direct dream studies can be conducted only in man. So far we know only that there is a coincidence between increased dream time per night and increased brain serotonin by precursor consumption,[1,9-12] and decreased dream time and decreased brain serotonin content[1,9-12] mainly induced by reserpine.[13] Because of the several intermediary processes, assumption of an interrelationship between brain serotonin and dreaming is highly inferential.

The experiments described here represent an attempt to ascertain whether or not the latency of dream incidence shortens during a mild but acute increase of brain serotonin, since such decrease of latency would offer a far more direct evidence of an interrelationship between intracerebral serotonin release and incidence of dreaming. Since serotonin does not readily pass the blood-brain barrier,[14] one may either attempt increasing brain serotonin through consumption of a precursor substance or imitate such increase by introducing a competitive inhibitor. Because the time required for yielding brain serotonin after intake of a precursor is variable, intravenous infusion of a competitive inhibitor, LSD (lysergic acid diethylamide), seemed to be the procedure of choice. LSD readily passes the blood-brain barrier,[14] and in low concentrations LSD has been shown to induce a serotonin-like reaction from human brain.[14-24] LSD also usually increases the dream time if consumed before one falls asleep.[25,26]

Methods

Electroencephalograms and dream records were obtained from 2 subjects during eleven consecutive nights. Since the rec-

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TABLE I. Effect of LSD infusion on latency of paradoxical sleep and dreaming

Night: Serial Number	Night: Total Number	Infusion: Substance	Infusion: Time After Onset of Third REM, Start (Minutes)	REM Sleep (Onset — in Minutes): Infusion Length	REM Sleep (Onset — in Minutes): Time Since Third REM	Dreaming (Awakened —After Onset of): Fourth REM (Two Minutes)	Dreaming (Awakened —After Onset of): Third REM (Forty Minutes)
2, 3, 5, 7, 9, 10	6	Saline	30	60	90	Yes	No
4	1	LSD	30	19	49	Yes	...
6	1	LSD	40	15	55	Yes	...
8	1	LSD	50	10	60	Yes	...
2, 3, 5, 7, 9, 10	6	Saline	30	60	90	Yes	No
4	1	LSD	50	11	61	Yes	...
6	1	LSD	40	15	55	Yes	...
8	1	LSD	30	17	47	Yes	...

ords obtained during the first night are known to differ from those obtained during consecutive nights,[27] they were discarded. Before retiring, an intravenous infusion needle was inserted into the cubital vein and was left in place at least to the end of the fourth REM period. During the control nights (2, 3, 5, 7, 9, and 10) the subjects received an infusion of saline for ten minutes, starting thirty minutes after the onset of the third REM period. During the fourth, sixth, and eighth nights, LSD was infused in concentrations of about 5 gammas per minute. Infusion was started in one of the subjects thirty, forty, and fifty minutes after the onset of the third REM period during the fourth, sixth, and eighth nights respectively. This order was reversed in the second subject.

During the fourth REM period, the subjects were awakened every night by a taped instruction: "Tell me what is on your mind right now," repeated, if necessary, in thirty-second intervals until verbal reports were forthcoming. Similarly, thirty minutes after the fifth REM period, the subjects were also wakened to learn about the content of the reports during a non-REM period. The reports were taped, and the tapes were evaluated by two unbiased judges for presence of dream fragments. For several technical reasons, larger sampling of the population was not possible.

Results

The results are summarized in Table I. During the control nights, the latency of the fourth REM period and dreaming averaged ninety minutes. Dreams have not been reported from the non-REM periods by the 2 subjects. LSD infusion reduced the latency of the next REM period and dreaming to ten to nineteen minutes instead of the expected forty to sixty minutes.

Comment

The consistency and magnitude of the decrease of the latency of REM and dream incidence by LSD infusion warrant the assumption of a relationship between intracellular LSD (serotonin) increase and REM or dream incidence.

One may conceptualize the mechanism of action of LSD and serotonin in inducing dreams taking into account our knowledge based on human and animal experimentation. Content analysis of dreams of subjects with bilateral hippocampal lesions[28] and with Korsakoff's disease[29] and observations on the coincidence of dreams and specific frequency ranges of theta activity[30] led to the conclusion that dreaming is, at least partly, an awareness of the visual concomitants of processes related to memory storage and retrieval.[31] Seemingly, this continuously ongoing process is kept from conscious awareness through inhibitory processes, also represented by the theta activity. Measures decreasing this inhibitory activity result in dreaming.[30,31] Both serotonin and LSD, if locally introduced into the hippocampus, decrease the amplitude of theta activity by synaptic inhibition of the generation of the theta activity.[22,32]

The mechanism of action of serotonin and LSD in decreasing theta activity is effected

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in the following way: A prerequisite for theta activity is afferent reticular activity reaching the hippocampus via septohippocampal fibers across the intact medial nucleus of the septum.[22] Theta waves result from an oscillating dipole across the pyramidal cell bodies and the distal region of their apical dendrites.[22,23,33] Since the synapses of the pyramidal cells and their axon collaterals are supplied by the basket cells, theta activity is prevalently inhibitory, mixed, at times, with weaker excitatory stimuli from the excitatory synapses of the apical dendrites.[33] The hippocampal synapses are cholinergic.[22,34] Under physiologic conditions, acetylcholine and serotonin are stored in the hippocampus, usually inside the same presynaptic terminals in adjacent structures.[35,36] Release of serotonin into the presynaptic intracellular space or entrance of the infused LSD into these spaces initiates a massive calcium ion transport from the synaptic cleft into the presynaptic terminal, causing a reversal of the calcium ion gradient across the synaptic surface of the presynaptic membrane.[6,8,14] Since acetylcholine release into the synaptic cleft against a changed calcium ion gradient is impeded, decreased synaptic transmission occurs, resulting in a decrease of the amount of theta activity generated. Presynaptic restorage of serotonin is followed by normal redistribution of the calcium ion, and, therefore, free acetylcholine release into the synaptic cleft and normal synaptic transmission, resulting in increased generation of theta activity. The latter amount of theta activity contains the necessary inhibition sufficient to keep the processes represented by dreaming out of awareness, and we stop dreaming for awhile. It is, therefore, proposed that dreams are perceived as a result of this serotonin-dependent chain reaction and vanish after restorage of serotonin. This assumption is supported by the results of wide-scale research revealing that during the process of falling asleep, not only is intracerebral serotonin released,[2-4] but also, all the 200 human subjects reported experiencing some form of hypnagogic hallucinations.[37]

Dreams and hallucinations share several qualities. Since hallucinations occur only during unusual cerebral conditions, these conditions may be responsible for the differences of the other qualities. Should these intracerebral processes affect the wave shape of the read-out signal,[38] the memories retrieved from old memory stores will differ accordingly. Since LSD modifies various cerebral processes, the hallucinations may reflect a combined effect of these changes, some as yet unidentified. According to the mechanism described, LSD will temporarily decrease some inhibitory mechanisms responsible for keeping many cerebral processes from conscious awareness. This would result in dreaming during sleep and in hallucinations during wakefulness. The assumed connection between dreams, hallucinations, and memory storage and retrieval processes is further substantiated by LSD hallucinations being heavily loaded with old memories.[39] The LSD-induced changes in the activity of sensory neurons may easily result in fluctuating changes of the memory retrieval signals, leading to the constantly changing quality of LSD mentation.[40] The decrease in LSD mentation of components dependent on neocortical activity results from direct inhibition of neocortical synaptic activity.[41] The scintillating geometric quality, specific for LSD hallucinations, results from the local effect of LSD on the retina,[42] perhaps also on other structures of the visual system.

Summary

LSD infusion during sleep decreased the latency of both the incidence of REM and of dreams in man.

A psychophysiologic mechanism capable of inducing dreams and hallucinations has been described. Dreams are viewed resulting, in part, from awareness of the visual concomitants of processes related to memory storage and retrieval. Perception of these continuously ongoing processes is kept from awareness by special inhibitory mechanisms, for instance, theta activity. Temporary and periodic decrease of these inhibitory processes during sleep may result in dreams. A serotonin-dependent biochemical chain reaction has been identified capable of modifying synaptic transmission in cholinergic hippocampal structures resulting in changes in the generated theta activity, and, therefore, leading to dreams. Restorage of serotonin results in termination of dreams.

Some of the processes contributing to LSD hallucinations have also been identified. Perception of processes related to memory storage and retrieval due to decreased theta activity during wakefulness may result in hallucinations. Direct effect of LSD on sensory stimuli affecting retrieval may contribute to the quality and content of the retrieved processes. Direct inhibition of neocortical synaptic activity may be responsible for some changes in the quality of mental attitudes characteristic of LSD. The scintillating geometric components, unique for LSD hallucinations, appear to result from direct effect on LSD on the retina and perhaps also on other structures of the visual system. These effects of LSD during sleep will induce dreams and during wakefulness may induce hallucinations.

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