1.6 THE MOLECULAR-BIOLOGICAL LANDSCAPE

1.6.1 WHICH RECEPTORS?

M's recall was initiated by the preferential binding of LSD to certain serotonergic (5-HT) that are broadly distributed throughout brain and body, including the gut and placenta. LSD binds to several 5-HT receptor subtypes: 5-HT1a/1b/1d, 5-HT2a/2c, 5-HT5a, 6 and 7 (see Nichols, 2004 p. 161 and cited references therein). For M's LSD experience and recall of skull sensations, the most highly suspect LSD receptors are the 5-HT2a and the 5-HT1a, which are thought to exhibit quite different properties with LSD binding. The 5-HT2a receptors mediate an excitatory response to the pyramidal neurons within the cortical layers of the prefrontal cortex. It is these cortical receptors that are thought to be responsible for hallucinogenic inebriation, e.g., the visionary, reflective and spiritual realms. The 5-HT2c is often included with the 2a, owing to its close association in cue discrimination studies on rats (cf Glennon et al, 1983).

The 5-HT1a of the raphe nuclei will be the centerpiece of this monograph, owing to its control of subcortical memory postulated to be within the brainstem. Unlike the 2a, the 1a subtype mediates an inhibitory response and, although the 5-HT1a receptors co-exist with cortical 5-HT2a receptors in the cerebral cortex, their location for specific brainstem functioning may be exclusively within the raphe nuclei of the brainstem's reticular formation. The1a agonist, 8-OH DPAT (8-hydroxy-2-(di-n- propylamino) tetraline)) and its antagonist, WAY 100 635 are used routinely to study the inhibitory effects of raphe nuclei on target functions mediated by both cerebral and subcortical elements (cf. Brown et al, 2009). However, a few anatomical studies raise questions about the function of the raphe nuclei, reporting that 1a receptors may be elsewhere in addition to the raphe (Rodrigo-Argulo, 2000; Brown et al, 2008).

Apparently, LSD- 5-HT1a binding is non-hallucinogenic. For example, a structural analog of LSD, lisuride, is a potent and selective agonist for 5-HT1a and is non-hallucinogenic (Egan et al., 1998, Marona-Lewicka et al., 2002). Binding of LSD to the1a receptor in the raphe nucleus strongly inhibits the firing of its serotonergic neurons by direct or systemic application (Aghajanian et al, 1968, 1970, 1972). Endogenous hallucinogens, notably dimethyltryptamine and 5-methoxy DMT, bind to the 1a with high affinity and inhibit the firing of the dorsal raphe serotonergic axons (Aghajanian and Haigler, 1975). These hallucinogens are considered as agonists (promoters) although raphe neuron activity itself is suppressed. The dorsal raphe, one of 7 or 8 raphe nuclei in this area supplies over 90% of 5-HT projections to the brain.

A curious property of LSD is its relatively weak effect at the 5-HT2a receptor to stimulate second messenger systems, while it is the most potent drug for the hallucinogenic state mediated by the 2a/2c receptors (Nichols, 2004). This may be related to the response of excitatory glutamate receptors connected to the function of 2a/2c. LSD and the endogenous hallucinogens, DMT and its congeners are indoles (tryptamines) having high affinity for the 5-HT1a receptor (McKenna et al, 1990). Notably, the 1a and 2a receptors are affected by other neurotransmitter systems, e.g., the cholinergic and GABAergic influence on he 5-HT1a receptor (Haddjeri et al, 2000). Significant neurotransmitter systems, other than 5-HT, respond to LSD. The dopamine (DA) system within the caudate nucleus and the nucleus accumbens is well known for its relationship to addiction as pleasure centers and for its alleviation of Parkinson's symptoms including another site, the substantia nigra. The caudate and the acumbens have binding sites for indoles. While LSD binds to both DA receptors, D1 and D2, with a preference for the latter, it is not addictive.

1.6.2 THE COMPLEXITY OF 5-HT1A AND 5-HT2A FUNCTIONS

In accounting for M's LSD results in terms of the RaRN model, other neurotransmitter systems within the dorsal raphe itself must be involved: the inhibitory gamma amino butyrate (GABA) receptors, the excitatory alpha-1 adrenergic receptors and the excitatory glutamate receptors. One explanation would be that the LSD-bound 1a receptor activates the GABAergic suppression of these 5-HT neurons. Although this is unlikely (Aghajanian et al, 1972) there are several examples of this on issues of birth (Kaura et al, 2007) limbic (hippocampal) activity (Li et al, 2005) and REM sleep (Torterolo et al, 2000). These will be discussed later with respect to parturition with regard to activation of the hypothalamus. In any case, the interpretation will proceed with the fact that the indole hallucinogens suppress serotonergic neurons in the raphe nuclei at the 5-HT1a receptor, hypothetically to dis-inhibit reticular nuclei that control memory access in the brainstem. These same hallucinogens are excitatory in the thalamocortical regions as to their binding to the 5-HT2a/2c/glutamate complex.

The selection of a key receptor such as the raphe 5-HT1a is also shadowed by additional knowledge of receptor interactions that can diminish its certainty. The 5-HT 1a and 2a functions often appear to interact and can't be separated completely in certain cue discrimination studies (see Glennon et al, 1983 for method). In addition, the 2a function is clearly tied to the glutamate and dopamine receptors. Glutamate is released in the prefrontal cortex by a 2a agonist as a postulated mechanism for cortical excitation (Nichols, 2004 p. 147). While LSD discriminative cues involve the 2a receptor, momentary pre-treatment with LSD well before the test are mediated by the dopamine D2 receptor. In addition, LSD activates gene expression and metabolism at 2a sites. Another important research area is the influence hallucinogens have on changes in genetic expression, examined mainly by c-Fos immuno-histology, a break-through method that can determine new RNA synthesis at any given brain site (see the Biology of Parturition, below). With these complicating issues in mind, the model to be presented grows from the simpler basic idea that LSD binds to 5-HT1a to stop the firing of raphe 5-HT neurons and unblock nuclei of brainstem reticular formation. The concurrent involvement of 5-HT2a at birth is also important as a mental bolster for the mother and for activation of the hypothalamus (see below).

The consensus hallucinogenic 5-HT2a effect M experienced early in the session was dream-like and very brief. This little show was completely over before the sensory recapitulation that dominated throughout the rest of the LSD session. This is consistent with the findings that LSD is not a strong functional ligand for the 5-HT2a receptor (see McClue et al, 1989 and references therein), although LSD inebriation is more intense than that of other hallucinogens. Also, the opposition by the inhibitory 5-HT1a receptors in the same prefrontal cortical area would contribute to the brevity of this cerebral effect. The 5-HT1a receptor is found throughout the thalamocortical areas and coexists with 5-HT2a receptors in cortical pyramidal layers (however, see Nichols, 2004). Therefore, the memory of skull sensations is postulated to be located somewhere within a brainstem nucleus (probably the cerebellum) under the control of the raphe 5-HT1a receptor and DMT (or a derivative, 5-methoxy-N,N-dimethyltryptamine) as the endogenous raphe inhibitor. These and other possibilities for the identity of the endogenous hallucinogen are considered in detail below in 1.9, “What is the endogenous hallucinogen?”.

Support for 5-HT1a in functional venues such as birth and trauma in humans or primates might be found by extrapolation from similar 2a venues in rat models. Studies of hallucinogens as actors in parturition haven't been done. However, the antagonist to the 5-HT2a receptor (ketanserin) blocks the rat's cue to selecting the LSD lever in the discrimination test (above), but not for our much closer relative, the monkey (Nichols, 2004; Nielsen, 1985). Also, a mixed 5-HT1a/5-HT2 agonist, 5-methoxy DMT (one of the proposed endogenous hallucinogens) did provide the monkey with the LSD cue, reflecting the (dim) possibility that the 5-HT1a receptor for us primates may have the higher priority for LSD or EH function. Thus, certain functions involving 2a in the rat might involve the 1a in primates. For example, the secretion of supportive pituitary hormones at birth requires activation of the nuclei within the hypothalamus. As this involves 2a in the rat, it could involve 1a in the human at parturition (see Biology of Parturition, below). Aside from this hypothalamic suggestion, the receptor involved in both M's LSD recall and the EH mediated planting of the memory at birth is proposed to be the (non-hallucinogenic) 5-HT1a. In addition to the foregoing functional identification of individual raphe nuclei, the finding of high similarity between the indoles, DMT and LSD, as strong ligands to this receptor is consistent (Glennon et al., 1986).