The anhedonia hypothesis – that brain dopamine plays a critical role in the subjective pleasure associated with positive rewards – was intended to draw the attention of psychiatrists to the growing evidence that dopamine plays a critical role in the objective reinforcement and incentive motivation associated with food and water, brain stimulation reward, and psychomotor stimulant and opiate reward. The hypothesis called to attention the apparent paradox that neuroleptics, drugs used to treat a condition involving anhedonia (schizophrenia), attenuated in laboratory animals the positive reinforcement that we normally associate with pleasure. The hypothesis held only brief interest for psychiatrists, who pointed out that the animal studies reflected acute actions of neuroleptics whereas the treatment of schizophrenia appears to result from neuroadaptations to chronic neuroleptic administration, and that it is the positive symptoms of schizophrenia that neuroleptics alleviate, rather than the negative symptoms that include anhedonia. Perhaps for these reasons, the hypothesis has had minimal impact in the psychiatric literature. Despite its limited heuristic value for the understanding of schizophrenia, however, the anhedonia hypothesis has had major impact on biological theories of reinforcement, motivation, and addiction. Brain dopamine plays a very important role in reinforcement of response habits, conditioned preferences, and synaptic plasticity in cellular models of learning and memory. The notion that dopamine plays a dominant role in reinforcement is fundamental to the psychomotor stimulant theory of addiction, to most neuroadaptation theories of addiction, and to current theories of conditioned reinforcement and reward prediction. Properly understood, it is also fundamental to recent theories of incentive motivation.

Keywords: Dopamine; Reward; Reinforcement; Motivation; Anhedonia

INTRODUCTION

The anhedonia hypothesis of neuroleptic action (Wise, 1982) was, from its inception (Wise et al., 1978), a corollary of broader hypotheses, the dopamine hypotheses of reward (Wise, 1978) or reinforcement (Fibiger, 1978). The dopamine hypotheses were themselves deviations from an earlier catecholaminergic theory, the noradrenergic theory of reward (Stein, 1968). The present review sketches the background, initial response, and current status of the inter-related dopamine hypotheses: the
dopamine hypothesis of reward, the dopamine hypothesis of reinforcement, and the anhedonia hypothesis of neuroleptic action.

**THE HYPOTHESES**

The notion that animal behavior is controlled by reward and punishment is certainly older than recorded history (Plato attributed it to his older brother). The notion that an identifiable brain mechanism subserves this function was anchored firmly to biological fact by the finding of Olds and Milner (1954) that rats will work for electrical stimulation of some but not other regions of the forebrain. This led to the postulation by Olds (1956) of "pleasure centers" in the lateral hypothalamus and related brain regions. Brain stimulation studies by Sem-Jacobsen (1959) and Heath (1963) confirmed that humans would work for such stimulation and found it pleasurable (Heath, 1972). Olds (Olds and Olds, 1963) mapped much of the rat brain for reward sites, and even as his title phrase "pleasure centers" (Olds, 1956) was capturing the minds of a generation of students he was thinking not about isolated centers so much as about interconnected circuit elements (Olds, 1956; 1959; Olds and Olds, 1965). Olds (1956) assumed these to be specialized circuits that "would be excited by satisfaction of the basic drives – hunger, sex, thirst and so forth."

The first hints of what neurotransmitters might carry reward-related signals in the brain came from pharmacological studies. Olds and Travis (1960) and Stein (1962) found that the tranquilizers reserpine and chlorpromazine dramatically attenuated intracranial self-stimulation, while the stimulant amphetamine potentiated it. Imipramine potentiated the effects of amphetamine (Stein, 1962). Reserpine was known to deplete brain noradrenaline, chlorpromazine was known to block noradrenergic receptors, amphetamine was known to be a noradrenaline releaser, and imipramine was known to block noradrenergic reuptake. Largely on the basis of these facts and the location of reward sites in relation to noradrenergic cells and fibers, Stein (1968) proposed that reward function was mediated by a noradrenergic pathway originating in the brainstem (interestingly, Stein initially identified the A10 cell group, which turned out to comprise dopaminergic rather than noradrenergic neurons, as the primary origin of this system). Pursuing his hypothesis, C.D. Wise and Stein (1969; 1970) found that inhibition of dopamine-β-hydroxylase – the enzyme that converts dopamine to norepinephrine – abolished self-stimulation and eliminated the rate-enhancing action of amphetamine; intraventricular administration of l-norepinephrine reinstated self-stimulation and restored the ability of dopamine to facilitate it.

At the time of initial formulation of the noradrenergic theory of reward, dopamine was known as a noradrenergic precursor but not as a transmitter in its own right. At about this time, however, Carlsson et al. (1958) suggested that dopamine might be a neurotransmitter in its own right. The discovery that noradrenaline and dopamine have different distributions in the nervous system (Carlsson, 1959; Carlsson and Hillarp, 1962) appeared to confirm this assumption, and reward sites in the region of the dopamine-containing cells of the midbrain led Crow and others to suggest that the two catecholamine transmitters in forebrain circuitry – noradrenaline and dopamine – might each subserve reward function (Crow, 1972; Crow et al., 1972; Phillips and Fibiger, 1973; German and Bowden, 1974).

Evidence that eventually ruled out a major role for norepinephrine in brain stimulation and addictive drug reward began to accumulate from two sources: pharmacology and anatomy. The pharmacological issue was whether selective noradrenergic blockers or depletions disrupted reward function itself or merely impaired the performance capacity of the animals. For example, Roll (1970) reported that noradrenergic synthesis inhibition disrupted self-stimulation by making animals sleepy; waking them restored the behavior for a time, until the animals lapsed into sleep again (Roll, 1970). Noradrenergic receptor antagonists clearly disrupted intracranial self-stimulation in ways suggestive of debilitation rather than loss of sensitivity to reward (Fouriezos et al., 1978; Franklin, 1978). Also, noradrenergic antagonists failed to disrupt intravenous (IV) self-administration of amphetamine (Yokel and Wise, 1975; 1976; Risner and Jones, 1976) or cocaine (de Wit and Wise, 1977; Risner and Jones, 1980). Further, lesions of the noradrenergic fibers of the dorsal bundle failed to disrupt self-stimulation with stimulating electrodes