REVIEW

NEUROREGULATORY EFFECTS OF NICOTINE

OVIDE F. POMERLEAU¹ and JOHN ROSECRANS²

¹Behavioral Medicine Program, Department of Psychiatry, University of Michigan, Ann Arbor, Michigan, and ²Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, USA.

(Received 18 October 1988; in final form 3 July 1989)

SUMMARY

The impact of nicotine on the central nervous system is, in an important sense, neuroregulatory, with cascading effects on physiological and biochemical function as well as on behavioral activity. Accordingly, the neurotransmitter and neuroendocrine effects of nicotine constitute a critical part of its biological action, which includes reinforcing as well as pathophysiological consequences. This review focuses on nicotine's effects on cholinergic and non-cholinergic nicotine receptors and on the responses of catecholamines, monoamines, hypophysyal hormones, and cortisol. The contribution of critical variables, such as timing and duration of neuroregulator release and the patterns that make up the total response, is still largely unknown, particularly with regard to the effects of environmental context, history of nicotine use, and mode of administration. The evidence suggests that by altering the bioavailability of the above-listed neuroregulators, nicotine serves as a pharmacological "coping response", providing immediate though temporary improvement in affect or performance in response to environmental demands. Much of what is known to date is based on studies involving the administration of agonists and antagonists under different environmental conditions. Newer technological approaches such as autoradiography and positron emission tomography show potential for determining the neuroregulatory patterns involved and specifying nicotine's locus of action relevant to its behavioral and physiological effects.

INTRODUCTION

A REVIEW of the pharmacological effects of nicotine makes clear that the drug has powerful direct and indirect effects upon a number of neuroregulatory systems. In an important sense, the impact of nicotine on the central nervous system is neuroregulatory, with cascading effects on physiological and biochemical function as well as on behavioral activity (Balfour, 1982; Hall, 1982; Clarke, 1987; United States Department of Health and Human Services, 1988). Thus, the neurotransmitter and neuroendocrine effects of nicotine constitute a critical part of its biological action, serving to mediate potential pathophysiological consequences as well as reinforcement.

The present review will concern itself primarily with nicotine's neuroregulatory effects, describing recent research in both laboratory animals and humans. Nicotine's effects on cholinergic and non-cholinergic nicotinic receptors, as well as the responses of catecholamines, monoamines, hypophysyal hormones, and cortisol, will be highlighted. Of necessity, this review will examine findings based on a number of approaches and techniques, with dependent measures.
including iontophoresis, drug discrimination responding, electrocortical activity, autonomic responses, and overt behavior such as nicotine self-administration and free-field activity. For ease of presentation, effects on single neuroregulators will be emphasized, but it is important to note that there are extensive interrelationships among these substances (Meites & Sonntag, 1981; Tuomisto & Männistö, 1985). Research of the past decade has demonstrated that the relationships between neuroregulators and behavior are remarkably complex (cf., for example, Oades, 1985).

CHOLINERGIC EFFECTS

Sites of Action

Despite the large number of experimental studies conducted on the effects of nicotine in the central nervous system, the precise mechanisms involved in behavioral and physiological responses to the drug are by no means fully elucidated (cf. review by Balfour, 1982). Though nicotine has widespread peripheral actions, behavioral effects are primarily due to its central actions. The centrally active nicotine antagonist, mecamylamine, has been shown to block a number of nicotine's effects in animals (for example, reducing nicotine-produced seizures, startle responses, alterations in respiratory rate, Y-maze activity, and heart rate and body temperature changes in mice; Collins et al., 1986) and in humans (for example, reducing psychomotor performance enhancement and satisfaction from smoking, producing dysphoria, and increasing nicotine self-administration; Stolerman et al., 1973; Henningfield et al., 1983; Stolerman, 1986; Pomerleau et al., 1987). In contrast, quaternary blockers such as hexamethonium and chlorisondamine, which do not readily enter the CNS, are ineffective (Stolerman et al., 1973; 1983; Clarke & Kumar, 1983; Clarke, 1984; Collins et al., 1986).

Nicotine mimics certain actions of the neurotransmitter, acetylcholine. In the peripheral nervous system, it acts on two types of cholinergic receptors: autonomic ganglia receptors, which are antagonized by hexamethonium (C6, denoting the number of carbons between quaternary nitrogens), and neuromuscular junction receptors, where decamethonium (C10) is a selective antagonist (Paton & Zaimis, 1951). Nicotine functions as an agonist in low doses at these receptors but blocks transmission after initial agonist activity at high doses (Volle & Koelle, 1975). The evidence for C10 receptors in mammalian brain is equivocal, but most actions of nicotine that occur at behaviorally relevant doses can be blocked by C6-selective antagonists such as mecamylamine (Clarke, 1987). Stereoselective behavioral actions of nicotine have been reported, consistent with receptor mediation (Meltzer et al., 1980; Kumar et al., 1983; Garcha et al., in press). The reinforcing effects of nicotine and tobacco smoking appear to be mediated by C6 receptors in the CNS (Hanson et al., 1979; Tennant et al., 1984; Clarke et al., 1985). By way of explaining nicotine's biphasic effects (i.e., stimulation followed by inhibition of responding, particularly evident at high levels), Marks et al. (1983) and Collins et al. (1986) reviewed evidence supporting the possibility of agonist-induced conformational changes of the nicotine receptor to a desensitized form (Schwartz & Kellar, 1983), which could account for nicotine's ability to act functionally as an antagonist but mechanistically as an agonist.

Continuing progress is being made in characterizing the nicotinic cholinergic receptor, correlating molecular structure with functional properties (Conti-Tronconi & Raftery, 1982). This receptor was the first neurotransmitter receptor to be identified as a molecular entity, isolated and purified in an active form, and reconstituted in artificial membrane systems with quantitative retention of physiological properties. Of particular relevance to the understanding of tobacco smoking, recent studies have also demonstrated that nicotine binding sites in the human brain are stable in post-mortem preparations (Benwell & Balfour, 1985) and that these sites clearly function as nicotinic cholinergic receptors in saturation binding studies (Shimohama et al., 1985). The
possibility of a "nicotine-like" endogenous ligand has been raised (Sershen et al., 1984), based on the observation that mouse brain homogenates contain material that inhibits saturable binding of \(^3\text{H}\)-nicotine in mouse cerebral cortex. Finally, the possibility that nicotine also acts on non-cholinergic nicotinic receptors in the brain (Abood et al., 1981; Rosecrans & Meltzer, 1981) continues to be a subject of speculation (Clarke, 1987).

Nicotinic and muscarinic binding sites in brain have different biochemical characteristics and neuroanatomical distributions and are regulated in vivo by different cholinergic agonists (Marks & Collins, 1985). The functional independence of the two cholinergic systems has been demonstrated in various drug discrimination paradigms (Rosecrans & Meltzer, 1981). Interactions between the two systems also have been observed. For example, anatomical data suggest that some nicotine receptors in brain have a presynaptic location (Clarke et al., 1986), and there is evidence for nicotinic autoreceptors promoting acetylcholine release in the cerebral cortex (Armitage et al., 1968; Rowell & Winkler, 1984), and in the autonomic nervous system (Briggs & Cooper, 1982). Thus, at certain cholinergic synapses, nicotine may act presynaptically to release acetylcholine onto postsynaptic muscarinic cholinoreceptors (Chiou et al., 1970). Moreover, Weiler et al. (1984) have shown that presynaptic muscarinic neurons modulate post-synaptic nicotine neurons, at least in the neostriatum. Arrangements between neurons may vary within the cholinergic system; for example, both patterns may exist at hippocampal sites (Bird & Aghajanian, 1976; Segal, 1978; Rovira et al., 1983).

Thus far, the sites of nicotine action have been discussed without resolving the issue of whether C6 sites are physiological receptors upon which nicotine is acting, or whether they are merely nonspecific neuronal sites to which nicotine attaches itself. Furthermore, the question of whether central receptor entities are similar to those in the periphery should be resolved. Neither issue can be settled satisfactorily at the present time, but, taking the second question first, the fact that mecamylamine is an effective nicotine antagonist at both locations suggests that there must be similarities between CNS nicotine receptors and those in the autonomic ganglia.

With regard to the first question, there is evidence to show that sites bound by \(^3\text{H}\)-nicotine are sensitive to \(^3\text{H}\)-acetylcholine as well (Clarke et al., 1985). There is good correspondence between maps of nicotine and acetylcholine binding, and there is a close association between brain areas of increased cerebral metabolism (2-deoxyglucose) following physiological doses of nicotine (Grunwald et al., 1988; London et al., 1988). Thus, there appears to be a correlation between function and binding. A major difficulty arises, however, in comparing \(^3\text{H}\)-nicotine and/or \(^3\text{H}\)-acetylcholine maps with \(^125\text{I}\)-\(\alpha\)-bungarotoxin (BTX) binding sites (BTX has been used for a long time as a marker for mapping nicotine receptors). This heterogeneity may reflect the activity of two populations of nicotine receptors, each with different binding affinities (Harfstrand et al., 1988). Accordingly, \(^3\text{H}\)-nicotine and \(^3\text{H}\)-acetylcholine may label high affinity binding sites, whereas \(^125\text{I}\)-BTX most probably labels low affinity sites. The two receptor populations may mediate different effects (Collins et al., 1986; Wonnacott, 1987).

**Physiological Effects**

Nicotine's cholinergic effects are extensive. Among the physiological effects of nicotine-induced acetylcholine release (from the parietal cortex in cats) is desynchronization of the cortical electroencephalogram; reduced acetylcholine levels, observed after high doses of nicotine, are associated with decreased cortical activity (Armitage et al., 1968). A similar pattern of changes has been reported for the human electroencephalographic response to cigarette smoke (Remond et al., 1979). In conscious cats, there is evidence that atropine blocks the cortical activation but not the behavioral arousal seen in animals given intravenous nicotine (Hall, 1970). Accordingly, Balfour (1982) suggested that cortical arousal is mediated by acetylcholine release, but that
behavioral stimulation is either not mediated by acetylcholine release or does not depend upon the action of acetylcholine at a muscarinic receptor. Nelson et al. (1975) also showed that behavioral suppression induced by electrostimulation of the midbrain reticular formation (MRF) was attenuated by the subcutaneous (SC) administration of 100 mg/kg of nicotine. These workers suggested that the effect may reflect activation of nicotinic receptors located in the limbic system, and most probably, the hippocampus.

Studies involving intracerebral administration of nicotine have been employed to determine the loci of nicotine's action (e.g., Kamerling et al., 1982; Wu & Martin, 1983). While some of the effects obtained by the direct application of nicotine to the brain may differ from those produced by systemic administration, the technique is helpful in elucidating nicotine's cholinergic mechanisms of action. The injection of nicotine into the cerebral ventricles of cats, dogs, and rats has been shown to produce a variety of physiological effects, including changes in cardiovascular activity, body temperature, respiration, salivation, muscle reflex tone, and electrocortical indices of sleep and arousal, the direction and duration of effects depending on dose and baseline response parameters (cf. review by Hall, 1982). Concerning the locus of action for the stimulus properties of nicotine, Rosecrans (1988) has shown that nicotine's ability to establish discriminative control of behavior (via subcutaneous administration) is mediated by mecamylamine-sensitive cholinergic neurons located in at least two brain areas, the midbrain reticular formation and the dorsal hippocampus. Interestingly, the effects generated at hippocampal neurons were stereoselective, and (+)-nicotine was approximately 10 times less active than the (-)-isomer in generalization tests.

Complex dose-related behavioral effects also have been observed following the systemic administration of nicotine (Clarke, 1987), including changes in locomotor activity, operant responding and conditioned avoidance, nociception, aggression, and food and water intake. Of particular relevance to the understanding of reinforcement of smoking are reports from both animal and human studies of improvements in task performance, stimulus discrimination, learning, and memory, as well as reduction of fear and anxiety and modulation of arousal (cf. review by Pomerleau & Pomerleau, 1984).

Understanding nicotine's effects on neuroregulatory systems will require the ability to differentiate between neuroregulatory effects and mechanisms of action at specific cholinergic neurons, for many of nicotine's consequences are secondary to its cholinergic effects. The time-tested approach has been to use nicotinic (N-cholinergic) and muscarinic (M-cholinergic) antagonists. As initially demonstrated by Domino (1973) in the cat and more recently by Stolerman et al. (1983) and Rosecrans (1988) in the context of studying the discriminative stimulus properties of nicotine in the rat, mecamylamine is the most effective antagonist of nicotine, both in vivo and in vitro. The peripheral ganglionic blocker, hexamethonium, and the muscarinic antagonists, atropine and scopolamine, are less effective as nicotine antagonists. Nicotine acts on a select group of receptors centrally, and receptor interactions appear to be quite specific, resembling those of few other compounds. The exceptions are alkaloidal analogs such as cytisine and anabasine and the chemical stereo-isomers, 3-methyl-pyrridyl-pyrolidine and (+)-nicotine (Rosecrans & Meltzer, 1981; Stolerman et al., 1983; Abood et al., in press). Thus, nicotine and its analogs appear to constitute a class distinct from other psychopharmacological agents, and the comparison with other psychoactive drugs is not straightforward.

As the above discussion indicates, nicotinic cholinergic events are only the first step in nicotine's neuroregulatory effects on the nervous system. This is underscored by a study by Rosecrans (1987), using the drug discrimination procedure, which demonstrated that intact central dopamine (DA) function may be required to elicit the discriminative stimulus (DS) properties of nicotine injected into the hippocampus. Adding further support, a number of studies have demonstrated cholinergic modulation of central catecholamine activity by nicotine (e.g.,
Andersson, 1985). Though there is still disagreement about the precise mechanisms, nicotine has been shown to stimulate norepinephrine (NE) release in the hypothalamus by a calcium-dependent process that can be inhibited by prior administration of hexamethonium or acetylcholine (Hall & Turner, 1972; Westfall, 1974). The mechanism is similar to that of nicotine's effects on peripheral adrenergic nerve terminals (Westfall & Brasted, 1972). At high dose levels, nicotine stimulates norepinephrine (NE) release by displacing it from vesicle stores at sites outside the hypothalamus (Balfour, 1982). Of considerable interest for the understanding of nicotine's sympathomimetic properties and the enhancement of attention and arousal following smoking (Svensson, 1987) is the demonstration of a direct action of nicotine on the rat locus coeruleus via nicotinic cholinergic receptors (Egan & North, 1986).

**MODULATION OF SEROTONIN AND CATECHOLAMINE ACTIVITY**

*Interrelationships with acetylcholine pathways*

The anatomical localization and physiological/psychological importance of biogenic amines such as serotonin (5-HT), DA, and NE has been the subject of intense research over the last 30 years. It was not until 1966, however, that the classic studies of Dahlstrom and Fuxe (1966) revealed that these amine-containing neurons were localized in specific ascending projection systems; descending systems have also been described. The physiological integrity of these systems was further demonstrated by the investigations of Aghajanian et al. (1967) in which the stimulation of 5-HT cell bodies localized in the midbrain raphé nucleus elicited the release of this transmitter from nerve endings located in the more rostral forebrain. The recognition that these amine systems constitute a unique interneuronal communication system has played a central role in the understanding of underlying neurochemical mechanisms of behavior and has made possible improved strategies for treating specific psychiatric and neurological disorders.

The cholinergic system has undergone a similar analysis (Fibiger, 1982). Delineating specific cholinergic pathways has been more difficult because of the nature of the cholinergic system, but they do appear to have a similar organization and to interact with specific biogenic amine pathways. For example, Robinson (1983) has clearly shown that 5-HT and DA systems exert tonic control over acetylcholine turnover in both the hippocampus and frontal cortex: Lesions of the medial raphé nuclei increase the acetylcholine turnover rate in hippocampal sites, while lesions of the dorsal raphé elicit a similar effect in frontal cortical areas; evidence for DA control comes from the observation that the catecholamine neurotoxin, 6-OHDA, facilitated hippocampal acetylcholine turnover when injected into the DA-rich septal area. The research of Kellar et al. (1987) and others also suggests that some nicotinic receptors may inhabit a presynaptic site on certain DA and 5-HT nerve endings. In addition, Westfall et al. (1983) have shown that 1,1-dimethyl-4-phenyl-piperazinum iodide (DMPP)-induced stimulation of nicotinic receptors in the striatum facilitates the release of both 5-HT and DA in a tissue slice preparation; of importance is that this preparation is devoid of cell bodies, suggesting that these nicotinic cholinergic receptors are primarily presynaptic. Furthermore, hexamethonium, but not atropine, attenuated nicotine-induced amine release, indicating that these neurons are nicotinic rather than muscarinic in nature.

Thus, when discussing nicotine's effects on specific biogenic amine-containing neurons, one must bear in mind that these amine systems have many interconnections and that, even though a specific receptor may be stimulated, either activation or inhibition of a particular 5-HT, NE, or DA neuron may be the ultimate outcome. Conversely, the integrity of specific nicotinic cholinergic neurons may also be under the control of one of these biogenic amine-containing projection systems. Nicotine, for example, appears to produce its discriminative stimulus effect in at least one major brain area, the hippocampus. This site is rendered insensitive if DA neurons...
innervating this area are destroyed (Rosecrans, 1987). Therefore, the interrelationships of these amine pathways are extremely important to our understanding of nicotine's effects on behavior, and especially its effects on the neuroendocrine system, because of the central role that these amine systems play in the hypothalamic control of the pituitary.

**Effects on serotonergic neurons**

Research evaluating the relationship between nicotine and 5-HT has involved several different approaches. Hendry & Rosecrans (1982) compared the behavioral effects of nicotine in rats selected for differences in activity and 5-HT turnover. The hypothesis was that, depending upon the rate of 5-HT turnover, nicotine would alter behavior by either attenuating or augmenting the level of functioning of 5-HT neurons having inhibitory effects on behavior. A variety of different strategies have been adopted to test this hypothesis, but conclusive evidence that nicotine acts via some 5-HT mechanism has yet to be obtained. Despite the failure to demonstrate a relationship between behavior and nicotine-modulated 5-HT function, however, Balfour et al. (1975) observed that acute doses of nicotine were capable of attenuating hippocampal 5-HT turnover, an effect specific to the hippocampus. Fuxe et al. (1987), on the other hand, did not observe any acute changes in 5-HT function following acute nicotine dosing but did observe a significant reduction of 5-HT turnover following repeated doses (3 × 2 mg/kg every hr); however, this effect may have been due to the metabolism of nicotine to cotinine, since the reduction of 5-HT turnover was not attenuated by mecamylamine.

5-HT function correlates with some pharmacological effects of nicotine, and investigators have evaluated potential links between 5-HT and neuroendocrine function. Balfour et al. (1975) were among the first to show a relationship between 5-HT and nicotine's ability to induce the release of plasma corticosterone, presumably via activation of the pituitary-adrenal axis. Basic findings from ensuing research were that (1) a reduction in 5-HT turnover (correlated with an increase in plasma corticosterone) followed acute nicotine injections in the rat; (2) rats exhibited tolerance to pituitary activation following repeated nicotine doses, but not to the attenuation of hippocampal 5-HT turnover; (3) psychological stress antagonized nicotine-induced reductions of hippocampal 5-HT; and (4) nicotine inhibited the normal adaptive response to adrenocortical stimulation following chronic stress (Balfour et al., 1986). These data suggest that nicotine can modify the way in which rats adapt to stress, which may be mediated by changes in hippocampal 5-HT function. At this point, however, it is difficult to draw any firm conclusions concerning how nicotine affects 5-HT neurons and whether this neurotransmitter is uniquely involved in any of nicotine's effects on neuroendocrine function. The fact that hippocampal 5-HT turnover appears to be selectively attenuated by nicotine, combined with the fact that this brain area has a high concentration of nicotinic cholinergic receptors, is nonetheless an important finding that should be further studied and evaluated.

**Effects on noradrenergic and dopaminergic neurons**

Attempts to determine whether nicotine produces any effects on NE-containing neurons have met with mixed success. Earlier work suggested that nicotine may affect behavior via an NE component, but subsequent research was not supportive of such claims (Balfour, 1982). Svensson (in press) provided evidence that NE neurons located in the locus coeruleus are activated by nicotine centrally, resulting in sympathetic activation. The ability of nicotine to alter DA function has been the subject of numerous investigations. As outlined above, investigators have observed that nicotine is capable of releasing DA from brain tissue (Westfall et al., 1983). Lichtensteiger et al. (1982) also observed nicotine to release DA through an acceleration of the firing rate of DA cell bodies located in the substantia nigra zona compacta when administered via iontophoretic application or SC (0.4–1.0 mg/kg). This activation was marked by a significant increase in striatal
DA turnover; dihydro-β-erythroidine, but not atropine, attenuated nigrostriatal activation. Evidence that nicotine facilitates the firing of DA cell bodies by stimulating nicotinic cholinergic receptors has been strengthened by the work of Clarke et al. (1985), who showed a specific effect by nicotine on pars compacta cell bodies, which was antagonized by mecamylamine. In an investigation of the release of DA from synaptosomes, Connelly and Littleton (1983) noted that DA release lacked stereoselectivity but was antagonized by the ganglionic blocker, pempidine. Imperato et al. (1986) showed that these effects occurred in the freely moving rat as well as in vitro. In these studies, nicotine specifically released DA from the nucleus accumbens, as opposed to the caudate nucleus.

Other studies provide further information that nicotine can greatly influence DA function, as do several other drugs of abuse (Wesffall et al., 1983; Mereu et al., 1987). Studies involving either peripheral or intracranial injection into DA-rich areas — namely the substantia nigra pars compacta (A9) and the ventral tegmental area (A10) — indicate that nicotine can greatly facilitate firing rates of these neuronal sites, an effect antagonized by mecamylamine. Wesffall et al. (1983) and Mereu et al. (1987) suggested that the nicotine-induced stimulation of striatal and nucleus accumbens neurons (via the facilitation of A9 and A10 firing rates) was related to the removal of tonic inhibitory influences from adjacent non-DA neurons, i.e., GABA-inhibitory neurons. Thus, these relationships are quite complicated and appear to be related to interactions at several interneuronal connections, monoaminergic as well other amino acid systems.

A DA reward theory of drug reinforcement, based on observations of psychomotor activation common to a number of substances of abuse involving activation of DA pathways (medial forebrain bundle projections to limbic and cortical regions), has been proposed (Wise & Bozarth, 1987; Wise, 1988). The inclusion of nicotine is supported by the demonstration of nicotine stimulation of ventral tegmental DA neuronal activity (Svensson et al., 1986), consistent with evidence of nicotinic receptors on DA neurons (Clark & Pert, 1985). The implications of this theory for understanding nicotine's mechanisms of action are not worked out. Finally, from an entirely different perspective, Janson et al. (1988) proposed that nicotine may protect DA neurons from neurotoxic destruction under certain conditions, for example, retarding the development of Parkinson's disease or delimiting damage from the DA toxin MPTP (1-methyl-4-phenyl-2,3,6-tetrahydropyridine). The process may be the result of attenuation of DA neostriatal neuronal activity via desensitization of nicotinic receptors controlling DA turnover. How these observations fit into what is known about nicotine modulation of DA function is not clear, though it should be noted that most of the above studies were conducted with acute nicotine dosing and that different results might be obtained with repeated, chronic dosing. It is possible that nicotine may be acting as an antagonist of DA systems in the regular smoker by producing a chronic desensitization of DA receptors.

Fuxe and coworkers (Fuxe et al., 1986) have long been interested in nicotine's effects on central catecholamine neurons in relation to neuroendocrine function. Their measurements of amine function utilize quantitative histofluorometric techniques rather than the more classical neurochemical and neuropharmacological methods. The procedure involves measuring the disappearance of catecholamine stores by administering a tyrosine hydroxylase inhibitor (AMPT) to rats receiving various doses of nicotine or exposed to tobacco smoke; tissues are then exposed to formaldehyde gas, and histofluorescence in AMPT-treated rats is evaluated in comparison to controls. This procedure has served these workers well over the years and has provided important information concerning nicotine's effects on biogenic amine function.

Their findings clearly indicate that nicotine is a potent activator of both DA and NE neuron systems located primarily in the median eminence and in areas of the hypothalamus. These effects appear to result from a stimulation of nicotinic cholinergic receptors generally antagonized
by mecamylamine. Concomitant neuroendocrine changes include reduction of plasma prolactin, thyroid-stimulating hormone, and luteinizing hormone, and an increase in corticosterone, following intermittent nicotine dosing (4 x 2 mg/kg, SC every 30 min) or tobacco smoke exposure (rats were exposed from one to four cigarettes containing 2.6 mg and received eight puffs at 10-min intervals). It should be noted that nicotine doses of 0.3 mg/kg administered intravenously will induce an overall activation of the hypothalamic-pituitary axis, leading within minutes to an increase of both ACTH and prolactin that subsides within 60 min. Tolerance to the corticosterone increase was observed following repeated nicotine doses, but there was little evidence for an effect of nicotine on either the increase in DA or the decreases in prolactin, luteinizing hormone, and follicle-stimulating hormone. Restraint stress also was observed to increase ACTH, corticosterone, and prolactin and to reduce DA and NE levels in hypothalamic regions. Interestingly, this stressor attenuated nicotine’s activation of NE neurons but did not reverse its attenuating effects on prolactin.

From these studies, Fuxe and colleagues’ conclusion is that nicotine appears to modulate neuroendocrine activity via either NE or DA activation. The evidence suggests that alterations in NE function are more important to the control of the pituitary-adrenal axis, while DA turnover appears to be more crucial to nicotine’s effects on prolactin, luteinizing hormone, and follicle-stimulating hormone. An important implication of this research is that nicotine-induced effects do not appear to be merely a reflection of acute and/or chronic stress but are rather quite specific, involving nicotinic cholinergic receptors that are probably located on a presynaptic DA or NE neuronal site. These studies further indicate that similar nicotinic cholinergic receptors are located within both DA mesolimbic and DA neostriatal systems (Fuxe et al., 1987).

**STIMULATION OF PITUITARY HORMONES**

The administration of nicotine can modify the release of both neurohypophyseal (posterior pituitary) and adenohypophyseal (anterior pituitary) hormones (Bisset et al., 1975; Hall et al., 1978). Among the pituitary hormones whose levels are modulated by nicotine are arginine vasopressin (antidiuretic hormone) and its carrier protein, neurophysin I, as well as growth hormone, prolactin, ACTH, and β-endorphin/β-lipotropin. Each of these substances has complex physiological effects (Munck et al., 1984), and several have psychoactive effects (Kastin et al., 1979; van Ree & de Wied, 1981). Nicotine’s effects on these and related hormones will be reviewed next.

**Arginine vasopressin**

Arginine vasopressin, in addition to its antidiuretic effects (maintaining plasma volume in hemorrhagic shock; Munck et al., 1984), serves as potent general vasoconstrictor with a possible action on the coronary arteries (Waeber et al., 1984). Arginine vasopressin may also act as a neuromodulator in pathways that affect behavior. It has been shown to promote memory consolidation and retrieval in rats (Bohus et al., 1978), and though the findings are far from definitive, there are reports of memory enhancement following intranasal administration of a vasopressin analogue in both normal and memory-deficient humans (Le Boeuf et al., 1978; Legros et al., 1978; Weingartner et al., 1981). A nicotinic cholinergic receptor in the medial basal hypothalamus and a muscarinic cholinergic receptor in the neurohypophysis have been shown to mediate the cholinergic release of vasopressin (Gregg, 1985). Nicotine has been found to stimulate vasopressin release in a dose-related manner in both animals (Reaves et al., 1981; Siegel et al., 1983) and humans (Pomerleau et al., 1983; Dietz et al., 1984; Seyler et al., 1986).
The pro-opiomelanocortin (POMC) group of hormones

The POMC hormones have been shown to be released in response to stress [more precisely, in response to the homeostatic perturbations caused in large part by the primary (i.e., catecholamine) response to stress; Munck et al., 1984], as well as to corticotropin-releasing hormone (Krieger & Martin, 1981). One of the POMC hormones, ACTH, has a number of behavioral effects in addition to its physiological role in stimulating the release of steroids such as cortisol from the adrenal cortex. A provocative review by Bertolini and Gessa (1981) describes the "stretching-yawning syndrome" in animals, in which ACTH produces rapid cycling between sleep and wakefulness as well as sexual stimulation, grooming/scratching, blocking of opiate effects such as analgesia, and the enhancement of attention and stimulus discrimination. Similarly, endogenous opioids such as β-endorphin, in addition to having physiological functions such as potentiation of vagal reflexes, promotion of respiratory depression, lowering of blood pressure, and blocking of the release of catecholamines (Beaumont & Hughes, 1979; Schwartz, 1981), have powerful antinociceptive effects (van Ree & de Wied, 1981) and modulate neurotransmitter systems, leading to amnesic effects (Izquierdo et al., 1980; Introini & Baratti, 1984). Margules (1979) speculated that the primary function of the endogenous opioids is metabolic, conserving body resources and energy (cf. reviews by Amir et al., 1980; Millan & Emrich, 1981).

Nicotine stimulates the release of corticotropin-releasing hormone from the hypothalamus through a nicotinic cholinergic pathway (Hillhouse et al., 1975; Weidenfeld et al., 1983). Using an isolated perfused mouse brain preparation, Marty et al. (1985) demonstrated that nicotine stimulates secretion of β-endorphin and ACTH in a dose-related manner when applied directly to the hypothalamus, but not when applied to the pituitary. Nicotine administration also has been shown to increase the levels of plasma corticosterone, ACTH, and β-endorphin in a dose-related manner in rats (Conte-Devolx et al., 1981). Termination of chronic nicotine administration has been shown to reduce hypothalamic β-endorphin levels (Rosecrans et al., 1985). Corrigall et al. (1988) observed that naltrexone antagonizes nicotine-modulated behavior in mice, providing a link between nicotine stimulation of endogenous opioid activity and behavioral responses. Acute administration of nicotine has been shown to increase levels of plasma ACTH and corticosterone sharply (Cam & Bassett, 1983), while chronic exposure results in complete adaptation (Cam & Bassett, 1984).

Freund et al. (1988) observed that mouse strains vary greatly in their corticosteroid response to acute and chronic nicotine administration. Pauly et al. (1988) extended this research on corticosteroid modulation of physiological and behavioral sensitivity to nicotine: Nicotine cholinergic receptor number was unaffected and nicotine metabolism was unchanged by adrenalectomy in mice, but sensitivity to the effects of nicotine was greatly enhanced. These changes could have been due to lack of adrenocortical hormones or to increases in brain concentration of ACTH and/or CRF as a result of loss of corticosteroid feedback inhibition (McEwen et al., 1986), but administration of corticosterone restored protection to nicotine in adrenalectomized mice (i.e., it brought sensitivity to nicotine back to the levels of sham-operated animals).

In humans, Risch et al. (1980; 1982) accumulated evidence for the cholinergic control of cortisol, prolactin, and β-endorphin release. Consistent with these findings, Pomerleau et al. (1983) and Seyler et al. (1984), in a series of studies on cigarette smokers, demonstrated significant, dose-related increases in circulating cortisol and β-endorphin following the smoking of two high-nicotine cigarettes after overnight deprivation; significant ACTH increases, however, occurred only with the nausea associated with very high plasma nicotine levels (Seyler et al., 1984). Under similar conditions, and in the absence of nausea, nearly identical plasma levels of ACTH, cortisol, and β-endorphin were observed by Novack and Allen-Rowlands (1985) in
response to smoking high-nicotine cigarettes.

With respect to other hypophyseal hormones, nicotine has been shown to inhibit the release of thyroid-stimulating hormone, prolactin, luteinizing hormone, and follicle-stimulating hormone in rats (Muraki et al., 1979; Andersson, 1985) and to enhance growth hormone secretion (Mendelson et al., 1981). In humans, smoking-induced stimulation of growth hormone and prolactin were reported by Wilkins et al. (1982); though no nausea was observed, fairly high plasma nicotine levels were achieved. Seyler et al. (1986) attempted to characterize the hypophyseal response pattern to cigarette smoking: After subjects smoked two high-nicotine cigarettes in such a way as to reach satiation (defined by the onset of nausea), significant elevations were found for prolactin, ACTH, β-endorphin/β-lipotropin, growth hormone, arginine vasopressin, and neurophysin I, in the absence of changes in the levels of thyroid-stimulating hormone, luteinizing hormone, or follicle-stimulating hormone. At somewhat lower doses and in the absence of nausea, the pattern of release was more selective, with significant elevations in arginine vasopressin, neurophysin I, and β-endorphin/β-lipotropin only; after two low-nicotine cigarettes, no observable changes in the circulating levels of the hormones occurred.

There is a need for further investigation of the factors controlling individual variability in the release of nicotine-stimulated hypothalamic and hypophyseal hormones associated with dysphoric states such as nausea (Seyler et al., 1986); such studies may shed light on the mechanisms by which nicotine intake is regulated and smoking behavior is reinforced (Kozlowski, 1980). It also should be noted that the onset of nausea following the first smoking experience may be an important factor in determining why some people take up smoking and others do not (Kozlowski & Harford, 1976). Susceptibility to nausea induced by nicotine or by other substances that stimulate the emetic center may provide an index of receptivity to smoking, and associated hormonal patterns may constitute an objective indicator of subjective effects.

The functional significance of nicotine-induced hormonal patterns and the role of neuroregulators in smoking is poorly understood. While there is an extensive literature on the use of agonists and antagonists to demonstrate relationships between cholinergic activity and particular behavioral effects (Henningfield et al., 1983; Kumar et al., 1987), and while similar strategies have been employed in the exploration of catecholaminergic contributions to smoking-related behavior, as reviewed above, the exploration of the contribution of neuroregulators to the reinforcement of smoking behavior is still at a very primitive stage.

For example, concerning the role of nicotine-stimulated endogenous opioid activity, Karras and Kane (1980) found that administration of the opioid antagonist, naloxone, resulted in a significant reduction in smoking behavior in a work setting; these findings have been replicated in a laboratory setting by Gorelick et al. (1989). Similarly, in a preliminary study, Palmer and Berens (1983) reported that naloxone blocked subjective pleasure from smoking. In a study that examined the role of endogenous opioid mechanisms in smoking, Tobin et al. (1982) had observed that mean inspiratory flow rate increases during the smoking of a cigarette but is depressed shortly after smoking; they administered naloxone and found that it had no effect on the initial stimulation of respiration in response to smoking but did significantly blunt the subsequent depression of respiration. On the other hand, in a carefully-designed parametric study in which naloxone dosage was varied systematically, Nemeth-Coslett and Griffiths (1986) were unable to demonstrate any systematic effect of naloxone on subsequent smoking behavior. The exact contribution of the endogenous opioids to smoking remains to be determined.

**IMPLICATIONS FOR UNDERSTANDING TOBACCO USE AS AN ADDICTION**

It is important to point out that nicotine's neuroregulatory effects are not fixed and invariant
but are dynamic, the product of interactions among environmental conditions, history of nicotine use, and behavior. Thus, under certain conditions, nicotine administration serves as a reinforcer, but under other conditions, nicotine can be used to punish self-administration (Barrett, 1983; Henningfield & Goldberg, 1983). As reviewed at some length by Benowitz (1988) and by Russell (1988), mode of administration is important in determining the effects that nicotine will have on behavior, with modalities like nicotine chewing gum or the transdermal patch producing slow nicotine rise-times, which foster tolerance, and other modalities such as cigarette smoking and aerosols producing a sharp rise in plasma nicotine, thereby overcoming tolerance. Specifically, nicotine’s biphasic pattern, in which the enhancement of arousal and alertness is followed by calming and tension-reduction, can be modified by changes in self-dosing (Gilbert, 1979; Pomerleau & Pomerleau, 1984), thereby achieving selective emphasis of one component or the other under the apparent control of demands of the setting (Warburton & Wesnes, 1979; Golding & Mangan, 1982; Rose et al., 1983) and/or personality characteristics (Myrsten et al., 1975). The neuroregulatory implications of these phenomena are not well understood. Nicotine’s biphasic effect on behavioral arousal has been known for some time; for example, Silvette et al. (1962) noted that lower doses of nicotine (200 to 400 μg/kg) stimulated spontaneous activity in rats, whereas higher doses (800 μg/kg) depressed this behavior. Rosecrans (1971) demonstrated that a 400 μg/kg dose produced maximal modulation, with acute doses stimulating more spontaneous activity in low activity rats than in high activity rats; nicotine-induced elevation of arousal level was directly related to inhibition of 5-HT turnover, suggesting that nicotine’s variable effects on the behavior of animals of different temperaments might be related to its effects on the forebrain serotonin projection system.

A biobehavioral analysis has been proposed to provide a framework for categorizing and evaluating the diverse findings on nicotine and smoking, as well as for guiding experimentation (Pomerleau & Pomerleau, 1984). The key elements of smoking — susceptibility, setting, behavior, and reinforcement — have been evaluated in terms of putative neuroregulatory components, highlighting the interactions between external environment and biological substrate in the control of nicotine self-administration and smoking (Pomerleau & Pomerleau, 1989). A fundamental premise is that by altering the bioavailability of certain behaviorally-active neuromodulators, nicotine serves as a pharmacological “coping response”, promoting immediate, temporary improvements in affect or performance (at the likely cost of delayed pathophysiological consequences).

Knowledge about the neuroregulatory mechanisms by which nicotine exerts its rewarding and health-damaging effects is incomplete and sketchy. For instance, the contribution of critical variables such as the timing and duration of release and patterns in nicotine’s neuroendocrine response, taking into account different environmental demands, history of nicotine use, and mode of administration, is still largely unknown. Much of what is known has been based on the administration of agonists and antagonists under different environmental conditions. Newer technological approaches such as autoradiography and positron emission tomography (Maziere et al., 1979; London et al., 1985; Kuhar et al., 1986) show potential for determining the neuroregulatory patterns involved and for specifying nicotine’s locus of action relevant to its behavioral and physiological effects.

Acknowledgements: Supported in part by National Cancer Institute grant CA/DA 42730 to Ovide F. Pomerleau and National Institute on Drug Abuse grant DA 04002 to John Rosecrans.
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