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Analgesia and Abuse Potential: An Accidental Association or a Common Substrate?

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FRANKLIN, K. B. J. *Analgesia and abuse potential: An accidental association or a common substrate?* PHARMACOL BIOCHEM BEHAV **59**(4) 993–1002, 1998.—The fact that centrally acting analgesics have abuse potential commensurate with their analgesic activity raises the question of whether these effects are related. The abuse potential of drugs depends on their ability to produce reinforcing effects, which are mediated by a neural system that includes the ventral tegmental dopamine cells and their connections with the ventral striatum. Morphine and amphetamine are both powerful analgesics and have high abuse potential. Their analgesic and reinforcing effects are mediated by similar receptors, similar sites of action, and overlapping neural substrates. These coincidences suggest that reinforcers may produce analgesia by transforming the aversive affective state evoked by pain into a more positive affective state. The implications of this hypothesis and its relation to other known mechanisms of analgesia are discussed. The hypothesis predicts that drugs with reinforcing effects should produce analgesia. A survey of drugs acting through 21 classes of receptors reveals that in 13 classes there is evidence for both analgesic and reinforcing effects that are approximately equipotent. The $GABA_A$ agonists were found to be the only drugs with confirmed abuse potential that lack analgesic activity. The interpretation of this and several other anomalous cases is discussed. © 1998 Elsevier Science Inc.

Reinforcement Analgesia Substance abuse Opioids Amphetamines Cannabinoids NMDA antagonists Serotonin GABA Dopamine

FOR more than 50 years psychopharmacological and pharmaceutical science has sought in vain for a highly efficacious centrally acting analgesic, lacking abuse potential, which might replace the opioids as the standard drug for severe pain. Many pharmacological classes of drugs have been screened, but candidates have proven to be either lacking in analgesic efficacy or to have abuse potential proportionate to their analgesic efficacy. Some years ago it was suggested that there might be a theoretical basis for the inconvenient fact that centrally acting analgesics have significant abuse potential—namely that abuse potential and analgesic efficacy are related (21,102). The underlying notion is that the affective state induced by drugs of abuse produces an indifference to pain, or affective analgesia—a state in which nociceptive input fails to arouse the distressing or aversive motivational state that it normally evokes (59). This hypothesis reflects the observations of clinicians and patients who have experienced the pain relieving effects of morphine (88). It has become more interesting as a neuropsychopharmacological hypothesis because our growing knowledge of the neural mechanisms underlying abuse potential, coupled with our knowledge of pain systems, permits the hypothesis to be rephrased in neurological terms (102). It is now believed that drugs are abused because they activate neural systems that have evolved to allow animals to learn novel behaviors to obtain biologically important objects (e.g., food or water) or interactions (e.g., reproduction). Psychologically, these events act as "reinforcers" to strengthen behaviors that lead to their occurrence. The affective analgesia hypothesis can be translated into the neuropsychopharmacological hypothesis that the neural substrate of analgesia and the neural substrate of reinforcement are at least partially overlapping. The minimal connection is that the neural substrate of reinforcement can drive the neural substrate of analgesia.

A stronger form of the hypothesis—that the two substrates are identical—cannot be sustained because research on pain has shown that there are multiple mechanisms of analgesia, and there is at least one neural system that induces analgesia that is driven by aversive events. This is the classic descending inhibitory control system (18). The normal function of this system is not fully understood, but it is established beyond any reasonable doubt that it can be activated by fear, anxiety, and other aversive states (9), as well as by opioids and a variety of nonopioid analgesic drugs (18,100). One function of this system is to inhibit nociceptive input in the spinal cord, and thus prevent nociceptive information being relayed to higher levels of the nervous system. Presumably it has evolved to optimize the animal's chances of survival in fight or flight situations, in which the normal withdrawal reflexes and voluntary

responses to nociceptive stimulation would seriously interfere with the smooth execution of complex escape and aggressive behaviors. It is possible that this system is a final common path for analgesia, and that it is activated in positive affective states as well as aversive states. There is evidence suggesting that this is not the case, but a digression to a brief discussion of pain tests and the neurology of pain is necessary before this evidence is considered.

A major problem in studying the mechanisms of analgesia is that there are a number of different ways to measure pain and analgesia in both animals and humans, and these do not yield similar results in all experimental situations. It is now widely accepted that there are multiple mechanisms of analgesia that operate at different levels of the nervous system. It is also accepted that the responses used as indicators in different pain tests are organized at different levels of the nervous system, and that they are differentially sensitive to the various analgesic and antinociceptive mechanisms.

It should be noted that responses to nociceptive input could be inhibited at any or all synapses between the receptor and the highest levels of sensory analysis (presumably the cortex or subcortical systems such as the amygdala and basal ganglia). In this regard, a distinction between analgesia and antinociception may be useful. It is suggested that antinociception refers to mechanisms that inhibit the transduction or transmission of sensory input from the nociceptors to the central mechanisms of pain perception. The term analgesia is often used in a more general way to refer to mechanisms that block motor and affective responses to nociceptive input, without necessarily implying inhibition of nociceptive input. The psychological implication of this distinction is that antinociception necessarily implies that perception of pain is blocked or attenuated. Analgesia, however, may be revealed as an altered tolerance to nociceptive stimulation without a reduction in the perceived intensity of nociceptive stimulation.

The tail-flick test is an example of tests that measure withdrawal reflexes organized in the spinal cord, and that can be evoked in the spinal animal. Because the neural circuitry for generation of the reflex is complete at the level of the spinal cord, these reflexes can only be inhibited if a drug acts locally in the spinal cord, or if it activates a descending modulatory system that innervates the spinal segment. We can, therefore, infer that this test is exclusively sensitive to local and descending antinociceptive mechanisms. Because it is the most studied pain test, it is not surprising that we know more about descending antinociceptive mechanisms than any other pain modulating systems.

Tests that depend on more complex responses, involving coordinated activity of muscles far from the site of nociceptive stimulation (e.g., locomotion, grooming, and vocalization), require both spinal cord and brain stem. The precise localization of the neural substrates is not known, but the responses can be evoked in more or less normal form by an animal that is decerebrated at the level of the pons (113). The most widely used tests in this category are the hot plate test and the formalin test. These tests would be sensitive to local brain stem influences, descending modulatory influences from forebrain to the brain stem, and from both of these to the spinal cord. These tests could also be sensitive to analgesics that affect the forebrain or brain stem but not the spinal cord. Such drugs could be analgesics that do not block the transmission of nociceptive input to the thalamus; in other words, drugs that are analgesic but not antinociceptive. One example is the dopamine (probably D_2) agonists, such as amphetamine and apomorphine. These drugs are efficacious in the hot plate and formalin tests, but are ineffective in the spinal reflex tests (10,120,156). Amphetamine is also reported to be a powerful analgesic in humans, and to potentiate the analgesic effect of opiates (27,51, 89). In humans D-amphetamine is approximately as potent as heroin.

More surprising is the effect of morphine in the decerebrate rat. In rats decerebrated at the level of the pons, both the tail-flick and formalin responses are exhibited. However, the effect of morphine on the formalin test is eliminated, while the tail-flick test still detects the antinociceptive effect of morphine (113). This implies that the population of cells that relay the nociceptive information essential for eliciting the response to formalin may not be identical to the nociceptive pathways inhibited by morphine at the level of the spinal cord. This inference receives support from a recent study showing that pharmacological block of some known descending inhibitory controls antagonizes the antinociceptive effect of morphine on spinal reflexes evoked by electric shock to the skin, but has little effect on the analgesic effect of morphine as shown by shock induced vocalization (25). Recent anatomical data also suggest that the neurons relaying nociceptive input from the spinal cord dorsal horn to the brain stem and thalamus may be separable from interneurons that relay nociceptive input from the dorsal horn to the spinal motor neurons that drive the tail-flick response (90).

Postshock vocalization, post stimulus behavioral distress, and human verbal report are measures that require the brain above the level of the pons, at least as high as the thalamus (33). These measures should be sensitive to all antinociceptive and analgesic mechanisms. Human verbal report can possibly distinguish between antinociceptive and analgesic mechanisms. There are anecdotal and experimental reports that opiates can relieve suffering without necessarily altering the perceived intensity of the sensory experience of pain, or the threshold for detection of nociceptive stimulation (62,81,138).

THE CHEMICAL NEUROANATOMY OF ANALGESIA AND REWARD

In support of the affective analgesia hypothesis, we have previously argued that two of the most powerful analgesics—amphetamine and morphine—can produce analgesia via known reinforcement mechanisms. Drug reinforcement is believed to be mediated by a neural system in which the mesolimbic dopamine pathway, linking the ventral tegmentum with the ventral striatum, is a key pathway. A variety of drugs (including mu and delta opioids, amphetamine, cocaine, cannabinoids, nicotine, and alcohol) are thought to produce reinforcing effects by stimulating the mesolimbic dopamine pathway, or by acting directly in the ventral striatum (40,63, 78,97,167). It has been shown that amphetamine produces analgesia in the formalin test by stimulation of the mesolimbic dopamine system. Amphetamine analgesia is blocked by dopamine D_1 and D_2 antagonists (121), and by lesions of the ventral tegmental area (VTA) and ventral striatum (VS) with 6-hyroxydopamine (37,120). It is tempting to speculate that dopamine also plays a role in the analgesic effects of other reinforcing drugs.

Morphine is a complex case because it is well established that morphine is antinociceptive through actions directly in the spinal cord, and through inhibitory controls descending from the periaqueductal gray and ventral medulla through the dorsolateral funiculus. These descending systems include fibers from noradrenergic, serotonergic, and probably GABAergic cell groups in the medulla (18,57). However, with low

doses of morphine, pain responses in the formalin test are inhibited by a mechanism that involves dopamine (120,121), does not involve serotonin (7), and does not pass through the dorsolateral funiculus (6). The fact that decerebration at the level of the pons or thalamus blocks morphine analgesia in the formalin test supports the notion that this analgesic influence arises from rostral structures (113,114). More recently, it has been shown that the amygdala is involved in the expression of this analgesia (108,115). To complicate the issue, there appear to be at least two sites for the rewarding effects of morphine. Reinforcing effects can be elicited by microinjections of morphine into either the VTA, or the PAG (26,36,45,129,158). Furthermore, the reinforcing effects of systemic morphine can be blocked by quaternary naloxone microinjected into either site (129). Likewise, analgesia in the formalin test can be elicited by morphine microinjected into the VTA and PAG, and systemic morphine analgesia is blocked by quaternary naloxone microinjected in these sites (109). Thus, there is direct evidence that the neural substrates of the analgesic and reinforcing effects of morphine are overlapping.

It is argued above, that the neural substrates of opioid and D_2 agonist analgesia overlap with the substrates of the reinforcing effects of these drugs, and this mechanism can be distinguished from descending inhibitory controls that mediate the antinociceptive effects of opioids and some other drugs. The questions then arise as to how the antinociceptive and affective analgesia mechanisms are related, and why some tests detect one and not the other? One hypothesis is that the conditions of testing can affect the degree to which various pain modulating systems are revealed by behavioral tests. There is strong evidence that the descending antinociceptive mechanisms are excited by stressors (9). Furthermore, morphine amplifies the antinociceptive effects of stress to such an extent that stress will enhance the effect of morphine even when the stress is too weak to produce detectable antinociception itself (12). Stress enhances morphine antinociception by facilitating the serotonergic component of the descending inhibitory system, but, when animals are tested under conditions that minimize situational stress, the contribution of a serotonergic component may not be detected (93,94). The formalin test also demonstrates opioid/serotonin-mediated inhibition of pain responses when animals are tested under mildly stressful conditions (2). Because formalin testing is usually done after prolonged habituation to the test environment, the stress potentiated antinociceptive effect of morphine is reduced, and the formalin test reveals forebrain-mediated analgesia that does not depend on serotonergic systems. Whether other descending systems are involved in the forebrain mediated analgesia remains unclear.

PHARMACOLOGICAL EVIDENCE FOR THE ASSOCIATION OF ANALGESIA AND REINFORCEMENT

The affective analgesia hypothesis can be formulated as a pharmacological hypothesis as well as a neurological one. If the neural substrates of affective analgesia and reinforcement are common, analgesia should be induced by drugs that have a reinforcing effect, and the analgesia will be mediated by the same receptor classes. Because there is a large number of transmitters, and an even larger number of receptor classes, the probability that two behavioral phenomena would have similar neuropharmacological profiles is quite low. The test can be further strengthened by adding the requirement that the analgesic and reinforcing effects should be in the same dose range. This additional criterion raises a number of methodological problems. Briefly, while there are reasonably good estimates of drug potency in various analgesia tests, dose–response analyses of reinforcement effects are rare, and different reinforcement tests yield different estimates of drug potency. On theoretical grounds, the effective magnitude of reinforcement of a drug treatment should be a function of both the true efficacy of the drug and the delay of reward imposed by the absorption kinetics. Thus, in a self-administration test, fast-acting drugs will appear to be more reinforcing (i.e., have higher abuse potential) than slow-acting drugs with similar affinity and efficacy at the drug receptor. By contrast, in the conditioned place preference (CPP) test the subject forms an association between the drug effect and the situational context (or place) in which the effect is experienced. If the drug effect is brief, it is not present much of the time (usually 30 min) that the association is supposedly being formed. Thus, any association formed during the period of drug effect will be in extinction for the rest of the conditioning trial. A much larger dose may maintain an effective drug level through the conditioning period, but the peak effect of the drug may then be high enough to produce aversive side effects. These aversive effects may also condition to the context, and reduce the apparent reinforcing effect of the drug. For these reasons the interpretation of discrepancies between the CPP test and self-administration tests in estimates of apparent reinforcing potency is problematic.

Table 1 summarizes the results of a search of the human and animal experimental literature for drugs that have been tested for both analgesic effect and abuse potential. A full discussion of the construction of Table 1 is beyond the scope of the present article, but the table was constructed by locating evidence that a drug was analgesic or antinociceptive, and then searching for evidence of rewarding effects, and vice versa. The results are, thus, not biased by excessive sampling from one cell of the table, although there is bias in the population of evidence, because more studies are published on substances that have strong analgesic or rewarding effects. The quantitative aspect of the comparison attempts to classify the efficacy of the drugs in regard to analgesia and abuse potential. Many drugs have only been tested on a small subset of the commonly used tests, and for others there is conflicting evidence. Furthermore, the hypothesis does not imply that all analgesic effects are mediated by reward systems. The effects of inhibiting inflammation, blockade of pain transduction at the peripheral nerve, and inhibition of pain transmission at the spinal level, would not be expected to involve reward mechanisms. The columns labeled "Notes" outline some of these restrictions to the scope of the comparisons.

It can be seen that, in the 21 drug classes covered in Table 1, there is a surprising degree of concordance between the two effects—both in terms of the drugs that produce the two effects, and those that produce neither effect. The association holds whether the drugs involved are agonists or antagonists at the receptors. For cholinergic muscarinic, adenosine, and NMDA receptors it is antagonists that have both analgesic and abuse potential. There were no instances found in which one effect was produced by agonists, and the other by antagonists. In most cases there was evidence (blockade by appropriate antagonist or agonist) that both effects were produced by the same putative receptor, and that they occurred in the same dose range. Overall, drugs with significant abuse potential, as shown by documented cases of drug abuse and by evidence of self-administration in animals, were clearly analgesic in human clinical experience and experimental tests. There were some drugs that were not included because their effects

TABLE 1

ASSOCIATION BETWEEN ANALGESIC EFFECT AND ABUSE POTENTIAL FOR 21 DRUG CLASSES

	Analgesia			Abuse Potential		
Drug Receptor		Notes	Source		Notes	Source
ACh nicotinic	+	human ischemic pain, rat tail flick	8,56,87, 137,142	++	humans and animals self-administer	46,69, 70,77
ACh muscarinic antagonist	+	human (historical); mice hot plate, tail flick	66,143	+	datura and antiparkinson drugs abused	29,151
Noradrenaline alpha-2	++	clonidine, xylazine in humans and animals	50,112, 131,149	+	humans and animals self-administer clonidine	42,49,169
Dopamine D_1	−	SKF 38393 inactive	23,121	−	SKF 38393 not reinforcing	83,170
Dopamine D_2	+++	humans and animals, experimental, and clinical pain	3,86,121, 162,172	+++	humans and animals self-administer	16,42,75, 135,165, 173
Dopamine D_3	−	7-OHDPAT −ve at D_3 dose, +ve D_2 dose in formalin test	60	−	7-OHDPAT −ve at D3 dose, +ve D2 dose	95
5-HT_2	+/−	descending spinal/peripheral (antagonist) antianalgesic in formalin test	5,7,53,62, 117,175	−	reduces amphetamine self-administration	32,68, 101,105
5-HT_3 (antagonist)	+	peripheral	67	−	antagonist no effect on cocaine self-administration	44
5-HT (tryptophan - 5HT_2 ?)	+/−	−ve in formalin, human postsurgical, +ve stress analgesia	7,62,71	−	reduces amphetamine self-administration	101,150
Opioid mu	+++	strong humans and animals, CNS, spinal, and peripheral	22,41,48,52, 153,171, 176	+++	humans and animals self-administer, CPP	39,43, 158,163
Opioid delta	++	intracranial	28,144,160	++	animals self-administer intracranially, antagonist reduces heroin self-admin.	45,126
Opioid kappa	+	probably spinal and peripheral	35,52, 133,153	−	pure agonists aversive	15,20
GABA (A)	+/−	barbiturates, benzodiazepines hyperalgesic, antiopioid	1,31,47, 61,130, 161	++	self-administered by humans and animals, barbiturates > benzodiazepines	39,43,125, 154,166
GABA (B)	+	baclofen antinociceptive (spinal)	82,139	+/−	self-administered but inhibits brain stimulation reward	55,72
NMDA (antagonist)	++	clinical and ischemic pain, veterinary	19,58,141	++	self-administered by humans and animals, CPP	104,110, 148,174
CCK (antagonist)	+	antagonists potentiate opioid analgesia	14,147	+/−	CCK(B) antagonist potentiates opioid CPP but no effect on self-administration	79,80
Cannabinoid (THC)	++	human clinical, formalin pain, weak in spinal reflex tests	111,118,122, 127,140	++	self-administered by humans and animals, CPP	103,116,159
Local anesthetic (unkown)	+	systemically	17	++	self-administered by humans and animals, CPP	39,152
Adenosine antagonist (caffeine)	+	enhance opioid and OTC analgesics	64,99,145	+	self-administered by humans and animals	39,43,84
Substance P	+	intracerebrally	11,38,146	+	CPP intracerebrally or systemically	98,128
OTC analgesics (COX inhibitors?)	++	antiinflammatory and CNS effects	34,65, 74,155	+	self-administered by humans, monkeys self-administer aspirin	4,84,124

+++ strong analgesic, high abuse potential, evidence from experimental and clinical or epidemiological data in humans and animals;
++ moderate analgesic or abuse potential, evidence from experimental and clincal or epidemiological data in humans and animals;
+ mild analgesic or abuse potential or incomplete evidence for the magnitude of the effects;
+/− inconsistent evidence, e.g., effects in some tests and not in others;
− lack of effect or countereffect.

span classes, and there is insufficient evidence as to their mechanism of action. One important case is ethyl alcohol, which has both abuse potential and a moderate analgesic effect in some tests (136,168). The abuse potential of alcohol may depend on an opioid mechanism linked to the VTA dopamine system (78). This would be consistent with it having analgesic effects like the opioids and DA agonists. However, ethyl alcohol also interacts with the $GABA_A$ receptor mechanisms, and it can be classified with the barbiturates in regard to its ability to increase pain related behavior in the formalin test (61).

The pharmacological analysis is also limited by the fact that the pharmacological characterization of reinforcing effects is much less detailed than is now possible for analgesic effects. For many drugs there is a lack of data about the receptors that mediate the effects, and many of the papers predate the identification of subclasses of receptors. Thus, the roles of DA receptor subclasses can be distinguished but, for example, $GABA_A$, adenosine, and 5-HT_2 receptor subclasses are not differentiated. In addition, there are many novel analgesic drugs that have been identified in animal tests (e.g., nitric oxide inhibitors, bradykinin antagonists, capsaicin analogues). Most of these drugs have not been used clinically, so that there is no evidence for abuse potential in humans. Neither have they been examined for reinforcing effects in animals.

In all, there were 12 classes of receptors positive for both effects. For these classes, the drugs with the most powerful analgesic activity are also those most highly rated as drugs of abuse, and are avidly self-administered by animals. Thus, mu opioids and dopamine D_2 agonists are the most readily self-administered, and appear to produce strong analgesia in clinical and experimental pain. The noradrenergic alpha$_2$ agonists, cannabinoid agonists, and NMDA antagonists have significant abuse potential, and sufficient analgesic efficacy to be clinically useful. The remaining classes of reinforcing drugs have some analgesic activity, and have sufficient abuse potential to produce occasional reports of abuse. Nicotine might be thought to show a large discrepancy between reinforcing and analgesic efficacy. In terms of its widespread and persistent use, it must be counted as a major drug of abuse, while its analgesic activity is detectable but not impressive. The difficulty of inducing nicotine self-administration in animals (69,76), however, suggests that its intrinsic reinforcing activity is low. Its widespread use may perhaps be explained by rapid nicotine absorption from smoking, which provides the smoker with countless repetitions of a small reinforcing effect with a very short delay of reinforcement. Nevertheless, in Table 1 it is classified as being more reinforcing than it is analgesic.

An intriguing case is the over-the-counter (OTC) analgesics such as aspirin and acetaminophen (paracetamol), and other nonsteroidal antiinflammatory drugs. These are believed to reduce inflammation by inhibition of the enzyme, cyclooxegenase (COX) (34). Their analgesic action is partly explained by their antiinflammatory effects, but there is evidence that they may also produce CNS-mediated analgesic effects (65,74,155). One member of this class, phenacetin, was withdrawn because of toxicity associated with abuse (124). OTC analgesics seem to be widely used for reasons other than relief of pain and fever, and users report that the drugs have mood-enhancing effects (4,106,123). Surprisingly, there is one report that monkeys will self-administer aspirin in a clinically effective dose (84).

The only case in which drugs have significant abuse potential and no analgesic activity is the drugs acting as agonists at GABA receptors. The barbiturates, and to a lesser extent the benzodiazepines, are well established drugs of abuse in humans, and are self-administered by animals (13,73). Although primary benzodiazepine abuse is quite rare, they are frequently used as adjuncts to opioids (107), and may enhance the rewarding quality of opioids (96). In animals, barbiturates and benzodiazepines will substitute for other reinforcing drugs (13), but self-administration in drug-naive rats and monkeys has also been demonstrated (39,43,125,154,166). The benzodiazepines and barbiturates seem to have no consistent analgesic effect when administered systemically (47,54,61, 161); rather, they may enhance responses to pain and antagonize the effects of morphine (1,31,54,130). The evidence is hard to interpret because, while the hyperalgesic effects of these drugs are probably mediated by $GABA_A$ receptors (1,132), there is little information about the mechanisms of their abuse potential. Moreover, because GABA is ubiquitous in neural circuits, GABAergic drugs may affect the same circuit at several levels. There is evidence that this is the case in pain mechanisms where $GABA_A$ agonists attenuate opioid activation of descending inhibitory controls in the brain stem, but facilitate them at the spinal level (30,91). The $GABA_B$ agonists are reported to have a spinal antinociceptive action, and there is one report that the $GABA_B$ agonist baclofen is self-administered (72). However, baclofen raises the threshold for rewarding effects of brain stimulation when injected into the VTA (55). Thus, the overall effect of GABA agonists given systemically is unpredictable without information about the locus of action.

The affective analgesia hypothesis does not require that all analgesic drugs have reinforcing effects, but it may be interesting to consider to what extent drugs lacking abuse potential may have centrally mediated analgesic effects. In four cases there was evidence that a drug was not reinforcing via a particular receptor, and evidence that there was no effect on pain (D_1 and D_3 receptors), or that antinociceptive effects were mediated directly in the spinal cord or in the periphery (5-HT_3 receptors, opioid kappa receptors). Opioid kappa agonists are reported to have analgesic activity, but they have aversive psychological effects that limits their use clinically (15,20,134). They are antinociceptive at the spinal level as well as peripherally at the site of injury (85,133,153). It should also be noted that the aversive effects of kappa agonists may be stressful enough to indirectly produce stress-induced analgesia.

There were two cases, the $GABA_B$ agonists (see above) and cholecystokinin (CCK) antagonists, in which drugs showed analgesic effects but there was inconsistent evidence for reinforcing effects. Antagonists of CCK consistently potentiate opioid analgesia (14,164). It was reported that a CCK_B antagonist strengthened, while a CCK_A antagonist blocked, reinforcing effects of opioids in the CPP paradigm (79). However, a later study found neither drug affected heroin self-administration (80).

There is evidence that 5-HT acting through 5-HT_2 receptors has antirewarding effects (see Table 1). Because 5-HT acting at 5-HT_2 receptors is so well established as an important component of descending inhibitory controls, this case was classified as positive for analgesia and negative for reward. Nevertheless, a number of trials have failed to find analgesic effects in human clinical pain and injury-produced pain in animals (7,62). More recently it has been shown that 5-HT_2 antagonists may be analgesic as a result of their ability to block the mechanisms by which inflammatory mediators stimulate nociceptive fibers at the site of an injury (5).

The dopamine D_2 antagonists are not listed, even though they have also been used as adjuncts to opioid analgesia with

claims that they potentiate analgesia (92). The DA antagonists vary from those that are mildly analgesic, like chlorpromazine, to those that produce hyperalgesia, like proethazine (24,92,119). In the rat, the selective D_2 antagonist pimozide has no effect on pain (121,157). Thus, the effects on pain do not seem to be correlated with D_2 antagonism.

To sum up, there is both neurological and pharmacological evidence of an association between reinforcement and analgesia. One might ask what could be the functional significance of such an association? In the case of the association between stress and analgesia, it is speculated that the inhibitory effects of stress on pain serve to increase survival by reducing competition between protective reflexes and the motor demands of flight and fight behavior. A similar competition may exist between protective and recuperative behavior and the behaviors evoked by natural reinforcers. Broadly, reinforcers evoke approach and consummatory behavior while pain evokes withdrawal or inhibits movement. Even an injured animal must sometime eat and drink, and there must be mechanisms for behaviors governed by positive incentives to overcome the powerful influence of nociceptive input. Drugs acting directly on the neural mechanisms of reinforcement may act as superreinforcers and disinhibit approach behavior from the restraining influence of pain.

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