Abstract Rationale: Research over the past decade demonstrating that NMDA receptor antagonists have the ability to inhibit opiate tolerance, sensitization and physical dependence has led to the suggestion that NMDA receptors may have a critical role in opiate-induced neural and behavioral plasticity. However, there have been suggestions that the effects of NMDA receptor antagonists on these phenomena result from non-specific behavioral or pharmacological effects, rather than from a specific inhibition of plasticity. Objectives: To review the literature in order to explore whether the effects of NMDA receptor antagonists on opiate-induced changes in behavior are best accounted for by an inhibition of neural and behavioral plasticity, or if alternative explanations might better account for the results. Results: The effects of NMDA receptor antagonists on the development of tolerance to opiate analgesia and the development of opiate physical dependence do not appear to be due to confounding behavioral effects produced by high doses of NMDA receptor antagonists, “side-effects” of a particular drug or drug class, blockade of associative learning processes, or state-dependency. Results on tolerance and sensitization to the locomotor effects of morphine are more mixed and controversial; however, there is evidence suggesting that NMDA receptor antagonists may inhibit these phenomena in a similar manner. Conclusions: NMDA receptor antagonists appear to inhibit the neural plasticity underlying some forms of opiate tolerance, sensitization and physical dependence, suggesting that NMDA receptors are involved in the development of these drug-induced changes in behavior. Further research will help to determine the neural mechanisms responsible for these phenomena, and the therapeutic potential for drugs acting on the NMDA receptor complex in the treatment of pain and addiction.

Keywords Opiate · Opioid · Tolerance · Sensitization · Physical dependence · Analgesia · Addiction · NMDA receptors · Excitatory amino acid · Plasticity

Introduction

It is now well established that excitatory amino acid systems are widely involved in neural and behavioral plasticity. N-Methyl-D-aspartate (NMDA) receptors, in particular, have been demonstrated to be involved in numerous examples of plasticity, including learning and memory (both acquisition and extinction), long-term potentiation, long-term depression, kindling, and neural development, among others (Collingridge and Lester 1989; McDonald and Johnston 1990; Coderre et al. 1993; Davis et al. 1993; Malenka and Nicoll 1993; Bear and Malenka 1994; Collingridge and Watkins 1994; Dickenson 1995; Abraham and Bear 1996; Bear 1996; Crepel et al. 1998; Michaelis 1998; Wheal et al. 1998; Yamakura and Shimoji 1999). The possibility that NMDA receptors might also be involved in neural and behavioral plasticity resulting from long-term treatment with psychoactive drugs arose just over a decade ago with the demonstration by Karler and coworkers (Karler et al. 1989, 1990) that NMDA receptor antagonists interfere with the development of sensitization to cocaine and amphetamine. This was soon followed by demonstrations that NMDA receptor antagonists interfere with the development of opiate tolerance (Marek et al. 1991a; Trujillo and Akil 1991a) and physical dependence (Trujillo and Akil 1991a). A key finding among these studies was that NMDA receptor antagonists interfered with the development, but not the expression of tolerance, sensitization or physical dependence. In other words, coadministration of the NMDA receptor antagonist with the target drug inhibited the acquisition of tolerance, sensitization or physical dependence, but administration of the antagonist after these phenomena had developed did not reverse their expression. This pattern of results offers support for the idea that NMDA
receptors are involved in the neural plasticity underlying the development of these behavioral phenomena. Since these initial reports, NMDA receptors have been implicated in several different forms of drug-induced neural and behavioral plasticity, including the development of tolerance, sensitization or physical dependence to a variety of psychoactive drugs, including amphetamine, cocaine, opiates, nicotine, ethanol, benzodiazepines, barbiturates and cannabinoids (see Herman et al. 1995; Kalivas 1995; Stephens 1995; Trujillo 1995; Trujillo and Akil 1995; Inturrisi 1997; Wolf 1998 for review).

Although the theory behind these experiments is sound, and the findings compelling, the idea that NMDA receptors are involved in drug-induced neural and behavioral plasticity has recently received criticism. Some researchers have suggested that other explanations may better account for the ability of NMDA receptor antagonists to interfere with changes in behavior produced by long-term administration of drugs of abuse (Carlezon et al. 1995; Wise et al. 1996; Tzschentke and Schmidt 1998; Vanderschuren et al. 1998). The purpose of this paper is to review the literature on the potential role of NMDA receptors in neural and behavioral plasticity arising from long-term administration of opiates, including tolerance, sensitization and physical dependence. The more specific purpose is to examine whether the effects of NMDA receptor antagonists on opiate-induced changes in behavior is best accounted for by an inhibition of neural and behavioral plasticity, or if alternative explanations might better account for the results. I have chosen to focus on opiates, since a thorough review on the role of excitatory amino acids in sensitization to psychomotor stimulants has recently appeared (Wolf 1998), and other papers in this volume are exploring related topics. Moreover, I have chosen to focus on studies that have examined mu opioids, since considerably more research has been done on these drugs than on drugs acting at other opioid receptors. I will begin by introducing the major alternative explanations for the effects of NMDA receptor antagonists on opiate-induced neural and behavioral plasticity. This will be followed by an exploration of whether or not these alternative explanations adequately account for the effects of NMDA receptor antagonists on different types of opiate-induced behavioral plasticity, including the development of tolerance to opiate analgesia, the development of opiate physical dependence, and the development of tolerance and sensitization to the locomotor effects of opiates. I will end with a summary, conclusions and suggestions for further research.

Alternative explanations for effects of NMDA receptor antagonists on tolerance, sensitization and physical dependence

Inhibition of neural and behavioral plasticity

The term plasticity refers to the capacity to change in response to experience. Neural and behavioral plasticity refers to changes in the brain and behavior that arise from experience. Tolerance, sensitization and physical dependence are robust examples of neural and behavioral plasticity. Long term experience with a drug leads to changes in behavior that are presumably mediated by changes in the brain. The ability of NMDA receptor antagonists to interfere with the development of opiate tolerance, sensitization and physical dependence has led to the conclusion that NMDA receptors are involved in opiate-induced neural and behavioral plasticity. According to this idea, activation of NMDA receptors, and the consequent calcium influx through NMDA receptor channels, may be required for the neuronal changes that underlie some forms of tolerance, sensitization and physical dependence (see Herman et al. 1995; Kalivas 1995; Stephens 1995; Trujillo 1995; Trujillo and Akil 1995; Inturrisi 1997; Wolf 1998 for review). However, it has been suggested that other explanations may better account for the ability of NMDA receptor antagonists to interfere with these phenomena. The three most prominent alternative explanations are drug “side-effects”, blockade of associative learning, and state-dependency.

Drug side-effects

One of the major criticisms that has been raised against studies of the role of NMDA receptors in opiate tolerance, sensitization and physical dependence is over the widespread use of the non-competitive NMDA receptor antagonist MK-801 (Vanderschuren et al. 1997, 1998; Tzschentke and Schmidt 1998, 1999; Wolf 1999). MK-801 is widely used as a tool in studies of NMDA receptor pharmacology for a variety of reasons – it is a highly potent and selective NMDA receptor antagonist; it readily crosses the blood-brain barrier and therefore has potent central actions following peripheral administration; and it is relatively inexpensive and commercially available. However, MK-801 and other drugs that have a high affinity for the non-competitive site of the NMDA receptor complex produce potent effects on ongoing behavior. For example, at moderate doses of MK-801 (0.15–0.3 mg/kg IP), an increase in locomotion is observed. At higher doses (0.3–1.0 mg/kg IP), the increase in locomotion is accompanied by stereotypy, incoordination and ataxia. At the highest doses (above 1.0 mg/kg IP), animals become limp and appear to be incapable of voluntary motor activity (Hirama et al. 1989; Tricklebank et al. 1989; Trujillo and Akil 1991a; Bubser et al. 1992; Danysh et al. 1994). Under certain experimental conditions these motoric effects may confound interpretations of behavioral experiments, especially those in which the primary measure is locomotion.

On the other hand, at low doses (0.1 mg/kg IP or below), MK-801 appears to be able to inhibit NMDA receptor function without significant effects on ongoing behavior. Similarly, other high-affinity non-competitive NMDA receptor antagonists have the ability block