Opiate Tolerance and Dependence
Roles of Receptors and Endorphins

LARS TERENIUS

1. INTRODUCTION

Opiates are not the only drugs that produce tolerance or dependence. However, tolerance to and dependence on these drugs develop very rapidly and reach a high magnitude. The clinical significance of opiate tolerance and dependence is well-known. Conditions for the use of these drugs are rigorously controlled and they can be used only on very strict clinical indications. Modern societies and less developed ones seem equally vulnerable to illegal abuse of these drugs. There is consequently a great need to define the basic conditions and mechanisms underlying opiate tolerance and dependence development.

Definitions and Scope

The focus of this review is biochemical mechanisms. It should be realized that, for instance, "dependence" in an isolated piece of intestine in an organ bath, as demonstrated by production of a contraction when naloxone is added, is a phenomenon which may have only some characteristics in common with the whole spectrum of dependence phenomena in humans. However, recent research has more and more emphasized the similarities between the physiology of synapses in the intestinal nerve plexuses and in neuronal populations in brain. These similarities extend to the neuronal circuitry as well as to the interaction between various neuronal systems. The similarities also hold across species. So far, virtually every system with opiate receptors has been found to show the phenomena of tolerance and dependence. Dependence is defined as a reaction
to abrupt withdrawal of opiate, or to antagonism by naloxone. Although this view is not proved, the standpoint taken here is that tolerance and dependence mechanisms at a biochemical level in various systems are similar. For obvious reasons, the review is limited to the direct targets for opiates, such as the opiate receptors (binding sites, transducing and effector mechanisms), the endorphinergic neurons, and the regulation of activity over the endorphinergic synapses.

Opiate tolerance and dependence have been investigated for many years. Before the discovery of the endogenous opiates (Hughes et al., 1975; Terenius and Wahlström, 1975), these phenomena were never attributed to a disturbance of an endogenous system but thought to be due to a highly artificial situation whereby foreign drugs caused changes in the normal balance between the various functions of the brain, in recent decades thought to be expressed in changes in neurotransmitter systems. The changes induced by the opiates might have been considered harmful just because the drugs were considered so artificial. Ever since the endogenous opiates, the endorphins, were discovered this is an untenable view. However, dependence to endogenous opiates does not seem to occur normally, whereas, for instance, one is definitely "dependent" on acetylcholine or insulin. Interference with the synthesis and/or release of these latter agents will lead to fatal consequences. This is because these systems have a vital function and are tonically active in carrying out this function. The functions of endorphins are definitely not vital: in fact, it is hard to establish any tonic activity in endorphin systems at all. The narcotic antagonist naloxone, even if it is not an ideal antagonist (e.g., it differs in affinity between different opiate subreceptors, see below), has been instrumental in the studies of the importance of endorphins. Naloxone will produce very mild effects on sensory thresholds, mood, and behavior, and fairly sophisticated experimental design is necessary to establish any effect at all. However, both acute and chronic administration of naloxone produce significant effects as will be discussed at some length below.

On the other hand, the dynamic range of the receptor–effector mechanisms in opioid systems must be considerable, since an opiate drug can cause powerful analgesia. It can also be shown that strong somatic stimulation can increase the release of opioid peptides into a spinal perfusate at least 30-fold (Yaksh et al., 1983). Thus, endorphin systems are intrinsically powerful, although they seem functionally dormant unless challenged. If an opiate is administered, it will perturb a system that normally operates at a very different and much lower dynamic range.

It may be worthwhile to give some thoughts to the time-scale for development of opiate tolerance and dependence. Declining receptor function occurring in fractions of a second (desensitization) or in minutes (tachyphylaxis) will not be considered here. In general, development of tolerance and dependence require from a few hours to a few days. In the former case it is customary to use the term acute tolerance (or dependence). On an even longer time-scale, chronic opiate administration will cause more or less permanent changes in higher CNS function—carryover effects—which may last for months or years. Short