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Review

Bidirectional translational research: Progress in understanding addictive diseases

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ABSTRACT

The focus of this review is primarily on recent developments in bidirectional translational research on the addictions, within the Laboratory of the Biology of Addictive Diseases at The Rockefeller University. This review is subdivided into major interacting aspects, including (a) Investigation of neurobiological and molecular adaptations (e.g., in genes for the opioid receptors or endogenous neuropeptides) in response to cocaine or opiates, administered under laboratory conditions modeling chronic patterns of human self-exposure (e.g., chronic escalating "binge"). (b) The impact of such drug exposure on the hypothalamic–pituitary–adrenal (HPA) axis and interacting neuropeptidergic systems (e.g., opioid, orexin and vasopressin). (c) Molecular genetic association studies using candidate gene and whole genome approaches, to define particular systems involved in vulnerability to develop specific addictions, and response to pharmacotherapy. (d) Neuroendocrine challenge studies in normal volunteers and current addictive disease patients along with former addicts in treatment, to investigate differential pharmacodynamics and responsiveness of molecular targets, in particular those also investigated in the experimental and molecular genetic approaches as described above.

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As the Laboratory of the Biology of Addictive Diseases at The Rockefeller University, and as an NIH–NIDA P60 Research Center, we are honored and delighted to join in the celebration of the 35th Anniversary of NIDA. Our report herein will focus on some accomplishments of our scientists over the last five years, since we were privileged also to write a scientific tribute to the 30th Anniversary of NIDA (Kreek et al., 2004b). Selected topics only will be covered herein, primarily ones of interest both from the standpoint of basic science findings, with potential implications not only for the addictive diseases, but also for the molecular neurobiological mechanisms underlying many other human disorders, including Parkinsonism, Alzheimer's and Huntington's disease, as well as many which further elucidate normal physiology. In addition, our studies, of course, have significant implications for specific addictive diseases.

1. *In vivo* effects of endogenous and synthetic opioids: translational application of non-human primate studies, and related human studies

Neuroendocrine markers can provide, in a non-invasive manner, direct information on the pharmacodynamics of endogenous and exogenous ligands, on the responsiveness of particular receptor systems, and on the function of particular neurophysiological systems. Many of these data can be obtained from human addiction patients or normal controls. However, studies in non-human primates may be especially valuable in producing data with more extensive designs (e.g., sigmoidal dose–effect curves and quantitative antagonism experiments) or pharmacological probes that are not available for clinical use (see also Weerts et al., 2007).

As part of the Laboratory's primary focus, we have studied the effects of opioid neuropeptides on a neuroendocrine biomarker (prolactin release) and compared it with selective exogenous ligands. Prolactin release is sensitive to both kappa- and mu-agonists, and is therefore a potentially useful biomarker for the pharmacodynamics of ligands active *in vivo* at these two systems relevant to the pathophysiology of addiction.

We and others have previously found that this neuroendocrine biomarker can provide quantitative information on the relative potency and apparent efficacy of kappa- and mu-ligands (e.g., Butelman et al., 2002). Selective delta-agonists appear not to be active in this regard (Butelman et al., 2002). Furthermore, some of the opioid receptors involved in this response in primates are thought to be located in hypothalamic areas functionally outside the blood–brain barrier. Overall, this therefore provides the relatively unique opportunity to quantitatively study *in vivo* the effects of neuropeptides that may have limited ability to cross the blood–brain barrier.

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1.1. Dynorphin A(1–17)

The endogenous full-length neuropeptide dynorphin A(1–17) (one of the main endogenous kappa-opioid ligands) was studied for its ability to stimulate prolactin release in gonadally intact female non-human primates (Butelman et al., 2004). Dynorphin A(1–17), given i.v. over a wide dose range, produced robust prolactin release, and exhibited a sigmoidal dose–effect curve (predicted by receptor theory, but rarely observed *in vivo*, due to experimental constraints). Intriguingly, in non-human primates, dynorphin A(1–17) was almost equipotent and equieffective to a synthetic high efficacy kappa-agonist U69,593, similar to its profile *in vitro*. This is therefore one of the unique situations in which an *in vivo*, non-invasive assay can be used to robustly study the pharmacodynamics of a natural sequence neuropeptide, compared with those of a synthetic agonist. Quantitative antagonism studies (apparent pK_B analysis) were carried out with naltrexone. This was consistent with the conclusion that kappa-receptors mediate the effect of dynorphin A(1–17) in this assay. Furthermore, the peripherally selective antagonist quaternary naltrexone (methylnaltrexone) blocked this effect of kappa-agonists, suggesting that opioid receptors outside the blood–brain barrier were involved. Such studies in primates using the full-length dynorphin A(1–17) neuropeptide can be a valuable comparison to studies with the dynorphin A(1–13) fragment, which has been used in human experimental studies (Kreek et al., 1999; Bart et al., 2003).

1.2. Nalmefene

Nalmefene is a mu-selective antagonist available as a parenteral pharmacological tool, for the blockade of opioid effects in humans. We evaluated whether nalmefene alone would have effect on prolactin levels in normal healthy human volunteers ($n = 33$) (Bart et al., 2005a,b). We found that systemic nalmefene doses (3 or 10 mg, i.v.) caused a significant increase in prolactin levels, compared to placebo. This suggested that nalmefene had a degree of agonist tone at either mu- or kappa-receptors. Studies in collaboration with the Laboratory of Dr. Jean Bidlack (University of Rochester) using the GTPγS *in vitro* assay determined that nalmefene is in fact a partial agonist at cloned human kappa-receptors, whereas it is solely antagonist at mu-receptors. Nalmefene's partial agonist effects at kappa-receptors may render it a particularly valuable tool for addiction pharmacotherapy, in that agonism at kappa-receptors is known to lower dopaminergic tone, which is known to be chronically affected by several addictive diseases.

1.3. Salvinorin A

As an illustration of the collaboration of the Center with related projects in the laboratory, we completed the first study on the neuroendocrine effects of the kappa-agonist hallucinogen salvinorin A (Butelman et al., 2007) (derived from the ethnomedical plant *Salvia divinorum*, now widely available in the United States) (see Roth et al., 2002). Salvinorin A is a diterpene, and represents a structurally unique new template for pharmacological probes of opioid receptors. Based on knowledge of kappa-agonist effects on the above biomarker, we studied the effects of a broad range of salvinorin A i.v. doses in non-human primates. Salvinorin A indeed caused robust dose-dependent prolactin release, with a very fast onset. Its potency and effectiveness were comparable to those of U69,593. Salvinorin A was sensitive to antagonism by nalmefene, at doses similar to those known to block kappa-receptor effects in primates. Furthermore, gonadally intact female subjects were much more sensitive to the prolactin-releasing effects of salvinorin A than males. Overall, the present studies provide some of the first quantitative and translationally viable *in vivo* pharmacodynamic data for this novel hallucinogen, and confirm its kappa-agonist profile in a primate species.

1.4. Beta-endorphin

As part of the systematic comparison, the effects of beta-endorphin were studied on this biomarker in non-human primates. Beta-endorphin is a major endogenous high efficacy agonist at mu-receptors, which also has affinity at delta-receptors, *in vitro*. Based on available background information on this system, beta-endorphin was directly compared to fentanyl (a high efficacy, centrally penetrating mu-agonist) and to loperamide (a mu-agonist which does not easily cross the blood–brain barrier). Both these compounds are in clinical use, and this further aids translational interpretation of these studies.

Fentanyl and loperamide both caused robust, dose-dependent prolactin release (fentanyl being approximately 10-fold more potent than loperamide). Surprisingly, beta-endorphin (0.01–0.32 mg/kg i.v.) produced relatively small effects on prolactin release, with 2 of 4 subjects showing almost no effect. Prior studies from other laboratories had detected effects of beta-endorphin on prolactin release (Foley et al., 1979; Catlin et al., 1980), but these are the first data that suggest a low potency and *in vivo* effectiveness of beta-endorphin in this regard. For this reason, we followed up these studies in two ways. Firstly, it is known that a particular single nucleotide polymorphism (SNP) in the non-human primate mu-receptor gene, C77G (Miller et al., 2004) has a reduced potency of beta-endorphin as its phenotype (intriguingly, this non-human primate SNP appears to be a functional ortholog of the human A118G SNP, discussed in the clinical section). However, none of these subjects had the C77G SNP. A further consideration was the potential rapid biotransformation of beta-endorphin into less active fragments. In collaboration with the Laboratory of Dr. Brian Chait (The Rockefeller University), we determined that full-length beta-endorphin was detected in these subjects until at least 5 min after injection, using a newly improved MALDI–MS method (Butelman et al., 2008). Likewise, we confirmed that the effects of loperamide could be completely blocked by the peripherally selective antagonist quaternary naltrexone, suggesting that a potential inability of beta-endorphin to cross the blood–brain barrier *per se* would not negate the possibility to be active in this biomarker assay. These studies therefore raise the possibility that the ability of beta-endorphin to mount an acute high efficacy action at mu-receptors *in vivo* may be limited.

2. Extracellular biotransformation of beta-endorphin in rat striatum and cerebrospinal fluid

In order to further understand whether beta-endorphin's agonist profile in the central nervous system (CNS) is highly related to the generation of particular biotransformation fragments, we investigated beta-endorphin biotransformation in the striatum of rats *in vivo*. These studies used a microinfusion/microdialysis technique coupled to MALDI–MS (developed in collaboration with the Laboratory of Dr. Brian Chait) (Reed et al., 2003). We observed rapid cleavage resulting in beta-endorphin 1–18, as well as several fragments resulting from further N-terminal degradation. *In vitro* studies with incubation of full-length beta-endorphin, with and without protease inhibitors, in the incubation fluid of isolated striatal slices indicate beta-endorphin is initially cleaved predominantly at the Phe18–Lys19 position, as well as at the Leu17–Phe18 position. Investigations of cerebrospinal fluid revealed similar enzymatic cleavage of beta-endorphin. The

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