The Opioid System and Food Intake: Homeostatic and Hedonic Mechanisms

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Abstract
Opioids are important in reward processes leading to addictive behavior such as self-administration of opioids and other drugs of abuse including nicotine and alcohol. Opioids are also involved in a broadly distributed neural network that regulates eating behavior, affecting both homeostatic and hedonic mechanisms. In this sense, opioids are particularly implicated in the modulation of highly palatable foods, and opioid antagonists attenuate both addictive drug taking and appetite for palatable food. Thus, craving for palatable food could be considered as a form of opioid-related addiction. There are three main families of opioid receptors (μ, κ, and δ) of which μ-receptors are most strongly implicated in reward. Administration of selective μ-agonists into the NAcc of rodents induces feeding even in satiated animals, while administration of μ-antagonists reduces food intake. Pharmacological studies also suggest a role for κ- and δ-opioid receptors. Preliminary data from transgenic knockout models suggest that mice lacking some of these receptors are resistant to high-fat diet-induced obesity.

Introduction

Opioids have been used as analgesics for centuries, and the use of opium as a tranquilizer agent has at least a 5,000-year history. In the 1970s, it was discovered that animals synthesized endogenous opioids [1]. Endogenous opioid peptides include endorphins, enkephalins, dynorphins, and endomorphins and act through three different receptors, μ-, δ- and κ-opioid receptor (MOR, DOR and KOR), which are members of a super-family of G
protein-coupled receptors. β-Endorphin is expressed in cells in the arcuate nucleus of the hypothalamus and in the brainstem. It acts via MOR and influences appetite as well as sexual behavior. Enkephalin is widely distributed throughout the brain and acts through MOR and DOR. Dynorphin acts via KOR and is found in the spinal cord and in many parts of the brain, including the hypothalamus [1].

Eating is not a simple, stereotypical behavior. It requires a set of tasks to be carried out by the central and peripheral nervous systems to coordinate the initiation of a meal episode, procurement of food, consumption of the procured food, and termination of the meal [2]. Most of these tasks are behaviors learned after weaning. Accordingly, there is now universal recognition that the CNS as a whole, rather than an exclusive center, i.e. the hypothalamus, is involved in the control of eating behavior. Among the large number of biological actions, the opioid system has been recognized as playing an important role in neural reward processes that lead to addictive behavior such as self-administration of opioid agonists directly and of other drugs of abuse such as nicotine and alcohol. Many of the neural structures involved in addictive behavior are also involved in food reward. Opioid receptor antagonists attenuate both addictive drug taking and appetite for palatable food. Data gleaned in recent years have shown that opioid antagonists, such as naloxone or naltrexone, decrease the intake of palatable food, whereas opioid receptor agonists, such as morphine or synthetic enkephalin analogues, increase food consumption. Acute administration of morphine and other general opioid agonist drugs increases food intake and weight gain in a naloxone-reversible manner. In contrast, chronic morphine treatment lowers food intake and body weight. Notably, chronic morphine administration led to a dysregulated feeding pattern, while injection of some of these agonists into the nucleus accumbens led to a greater increase in feeding of a high-fat diet in comparison to low-fat diet or carbohydrate-rich diets. The expression of MOR and the ligand preproenkephalin was increased in the nucleus accumbens, prefrontal cortex, and hypothalamus of mice from dams that consumed the high-fat diet. Taken together, these data imply a strong interrelationship among opiate pathways, body weight homeostasis, and nutrient intake, especially those that are rewarding [3]. This interrelationship has led to the concept that a dysfunction of the opioidergic brain may have a role in the pathophysiology of obesity and other disease states associated to altered body weight.

This review will be focused on the pharmacological and endogenous role of opioid receptors in energy balance and the mechanism mediating their actions (fig. 1). Moreover, we will summarize recent clinical trial studies that have shown promising results in obese patients. Understanding the precise role and mechanisms of the opioid receptors may lead to the identification of new potential targets directed towards specific hedonic pathways in both rodents and humans.

**Opioid Receptors and Feeding Behavior: Homeostatic and Hedonic Actions**

The opioid receptors are widely distributed throughout the central nervous system, and they are located in several brain areas related to the regulation of energy homeostasis. The role of opioid receptors in energy balance was demonstrated several decades ago (reviewed in [1, 4]). The first report showing that blockade of opioid receptors decreases food intake used naloxone, a general opioid receptor antagonist [5]. Since then, numerous studies have established that both systemic and intracerebroventricular administration of general opioid receptor antagonists reduces food intake and body weight in rodent models, including genetically obese Zucker and diet-induced obese rats [6–10]. Accordingly, agonists of the opioid receptors increase food intake [11]. In addition, the **MOR** gene, particularly geno-
types of rs1799971 in exon 1 and rs514980 and rs7773995 in intron 1, were positively associated with BMI and obesity [12].

Although the precise molecular mechanism by which opioids decrease food intake is not clearly understood, the central opioid and melanocortin systems are certainly interacting. Melanocortins are a family of proteins that reduce appetite, and their precursor, named pro-opiomelanocortin (POMC), encodes both alpha-melanocyte-stimulating hormone that decreases food intake and beta-endorphin that influence, among other things, mood and food intake. Interestingly, POMC neurons express postsynaptic MORs that are responsive to selective agonists which hyperpolarize POMC neurons and inhibit action potential firing. In addition, activation of the three opioid receptor subtypes, present in GABAergic terminals, inhibits the presynaptic POMC neurons. These post- and presynaptic effects of opioid agonists, together with the fact that POMC neurons synthesize and release an endogenous opioid, exemplify the important interrelationship between both systems, and led to the assessment of the nature of this interaction [13]. To decrease food intake, the melanocortins act mainly through two receptors, the melanocortin receptor 3 and 4 (MC3R and MC4R). The stimulation of food intake induced by agouti-related peptide (AgRP), an endogenous antagonist of MC3R and MC4R is reduced by the treatment with naloxone [14, 15]. The opioid receptors responsible for this interaction seem to be the MOR and KOR, since the blockade of both receptors together suppressed AgRP-induced food intake [16]. However, the blockade
of each opioid receptor separately did not modify the orexigenic action of AgRP [16]. The close interaction between the opioid and melanocortin system was further corroborated by the observation of the orexigenic effect of beta-endorphin (MOR ligand) being blunted by an agonist for MC3R and MC4R [17]. Accordingly, the treatment with a selective MOR antagonist suppressed the orexigenic action of an MC3R/MC4R antagonist [17].

Another key central mediator of feeding behavior and energy balance is neuropeptide Y (NPY). NPY and AgRP are co-located in the hypothalamic arcuate nucleus, and both neuropeptides are potent orexigenic factors. There are several reports showing that the orexigenic effect of NPY is dependent on the opioid system. For instance, central and peripheral administration of naloxone decreases NPY-induced feeding behavior [18–21]. The most important opioid receptors mediating the actions of NPY are MOR and KOR, as demonstrated by the fact that norBIN (KOR antagonist) and β-FNA (MOR antagonist) were efficient in blunting NPY-induced feeding, whereas naltrindole (DOR antagonist) did not modify NPY effects [18].

Orexin A is another orexigenic neuropeptide located in the lateral hypothalamus. Different reports have indicated that orexin-induced feeding behavior is modulated by opioids. Hypothalamic injection of orexin increased enkephalin gene expression in the ventral tegmental area, paraventricular nucleus and central nucleus of the amygdala, suggesting involvement in its orexigenic effect [22]. In keeping with this, naltrexone blunted the orexigenic action of orexin A [23]. Interestingly, naltrexone also blocked the effects of orexin A when it was directly administered in the nucleus accumbens, indicating that orexin needs to act through areas related to the rewarding properties of food to stimulate feeding behavior [23]. Contrarily, opioids are not mediating the orexigenic effects of melanin-concentrating hormone, another neuropeptide located in the lateral hypothalamus [24]. Another important finding was that the stimulation of high fat intake induced by the administration of DAMGO, a MOR agonist, in the nucleus accumbens required an intact orexin signaling in the ventral tegmental area [25], suggesting that the interaction between the opioid system and orexin modulates both homeostatic and hedonic pathways.

In addition to the regulation of food intake by homeostatic signals, opioids play an important role in the hedonic aspects of eating and reward mechanisms, modulating both the palatability of flavored solutions and food [26–28]. The acquisition of hedonic feeding involves the activation of the mesolimbic dopamine pathway, the dopaminergic projection from the ventral tegmental area to the nucleus accumbens, which is likely the most important mediator of the reward circuitry of food. Endogenous opioids regulate the mesolimbic dopamine pathway at both the levels of the ventral tegmental area and the nucleus accumbens [29]. Thus, most of the studies were performed injecting opioid receptor agonists/antagonists in these two regions of the mesolimbic dopamine pathway. Some reports suggest that the effects of opioids on the rewarding properties of food are more potent than their effects on the regulation of homeostatic signals. In this regard, naloxone suppresses intake of a sucrose solution more efficiently than the intake of water [30] and blocks the preference for a saccharin solution [31]. A similar decrease in preference for sucrose was also observed after treatment with naltrexone [32]. In contrast, the administration of DAMGO, a MOR agonist, in the nucleus accumbens increases saccharin intake [33], and the injection of DAMGO in the ventral tegmental area also elicits feeding response in completely satiated animals [34]. Opioids also modulate the preference for some specific diets in comparison to chow diet, as demonstrated by the fact that the treatment of rodents with naltrexone markedly reduces the intake of sucrose diet [35]. However, other laboratories have failed to demonstrate the interaction between opioids and food preference [36, 37] or the acquisition of a place preference associated with sucrose [38]. Furthermore, the opioid receptor antagonist naltrexone did not modify ghrelin-induced feeding in the mesolimbic reward pathway.
Ghrelin, a stomach-derived peptidic hormone that increases food intake, acts through the ghrelin receptor and is highly expressed within the hypothalamus, but also in different areas of the mesolimbic dopamine system. Thus, ghrelin stimulates feeding behavior when injected in the ventral tegmental area or the nucleus accumbens [39, 40]. However, pretreatment with naltrexone in the ventral tegmental area or the nucleus accumbens did not blunt the orexigenic action of ghrelin [39]. Therefore, these findings suggest that the opioid system is not essential for the actions of ghrelin on the rewarding properties of food, although future studies assessing effects at specific hedonic 'hotspots' in the brain are needed before firmer conclusions can be reached.

An important issue that must be addressed is the fact that most of the opioid antagonists have been reported to decrease short-term food intake, but few appear to reduce long-term intake. However, work focused on some synthetic opioid antagonists, the 3,4-dimethyl-4-phenylpiperidines, has demonstrated long-term efficacy. More specifically, LY255582, which in vivo acts as a MOR and KOR antagonist, decreased food intake and body weight over a 7-day period when injected intraventricularly once per day [41]. This compound also decreased food intake and body weight gain when administered subcutaneously to obese Zucker rats during a 30-day period of treatment [8]. Similarly, another report found that rats fed on high-fat diet receiving a chronic oral treatment with LY255582 for 14 days reduced body fat by decreasing food intake and stimulating lipid utilization [9]. Furthermore, LY255582 also inhibited the consumption of a highly palatable diet after a 4-day treatment and blocked the activation of mesolimbic dopamine neurons in the nucleus accumbens induced by high palatable diet [10]. Thus, LY255582 appears to be a potent and long-acting anorectic drug.

Opioids and Eating Disorders

Data gleaned recently have shown alteration in the expression of different neuropeptide and neurotransmitter pathways in neuropsychiatric conditions associated with behavioral abnormalities such as anorexia nervosa (AN) and bulimia nervosa (BN). Notably, the majority of patients with AN and BN exhibited auto-antibodies against alpha-melanocyte-stimulating hormone (α-MSH), a melanocortin peptide that decreases food intake and that is under the control of endogenous opioid peptides acting through both pre- and postsynaptic receptors [42]. In keeping with this, data obtained in experimental models support the hypothesis that opioids, in addition to being orexigenic per se (especially for palatable food) or able to modulate putative 'intrinsic' hedonic properties of foods, are also involved in learned-associative appetitive processes that underlie food acceptance and selection [43].

It has been proposed that AN arises as a pathological consequence of a primitive opioid-mediated mechanism in order to cope with unforeseen short-term food shortage, including mediation of the short-term energy balance adjustments or alleviation of negative mood associated with food deprivation. This suggestion can be tied into the potential role of opioids in stress-induced eating, but the complexity and inconsistent of the literature on pharmacological disruption of the opioid system in anorexia makes it difficult to fully evaluate this model. In addition, in humans, a reduction in MOR binding in the insula cortex in human patients with bulimia has been reported, and this was inversely correlated with fasting behavior. Whether this is due to a state-related down-regulation of the receptors subsequent to fasting or reflects a state of craving is still unclear. Also unclear is the impact of opioid antagonists in the treatment of bulimic patients where tests have produced discordant results.
While the case for the role of opioids in AN remains unclear, the case for a role in binge eating, defined as a maladaptive feeding behavior consisting of eating highly palatable, highly caloric foods that are rich in sweets, fats or both in a limited period of time, is more compelling. This is particularly relevant since as much as 6.6% of the normal population engage in binge eating behavior. Furthermore, binge eating behavior is also a key component of obesity. In fact, obesity is seen in 65% of patients with binge eating disorders with an increased progression over time and continued binge eating. The parallels between binge eating behavior and substance abuse were highlighted by Waller and colleagues [44], who emphasized that aspects of binge eating could meet the DSM III diagnostic criteria for substance abuse and who discussed the possibility that opioid dysfunction could underlie addictive binge eating. Data obtained in animal models have shown that the MOR and KOR antagonist, nalmefene not only attenuated binge behavior but also increased food intake of the less preferred diet. These effects are likely mediated by inhibiting MORs in the ventral tegmental area, leading to disinhibition of GABAergic interneurons and subsequently to decreased dopamine release in the nucleus accumbens.

Studies in bulimic patients treated with opioid receptor antagonists showed a reduction in the size and frequency of binging following naltrexone administration, and improvements in most patients’ binge-related indices. This included both the number of binges and purges as well as the ratio of binge to normal eating [45]. These antagonists also proved to be effective in reducing binge duration in bulimic patients and obese binge eaters, although some discordant results have also been reported. Though the reasons for these discrepancies remain unclear, it should be noted that a recent study has documented an increased frequency of the ‘gain of function’ G-allele of the A118G single nucleotide polymorphism of the MOR in obese patients with binge eating. These patients also reported greater scores on a self-report measure of hedonic eating [46]. Future studies with a robust phenotype and genotype characterization are needed in order to better define and uncover those patients that will benefit from treatment with drugs targeting the opioid system.

**Opioids and Food Intake in Humans**

Pharmacological studies of the role of opioids regulating feeding behavior in humans have been limited mainly to general opioid receptor antagonists such as naloxone (intravenously), naltrexone and nalmefene (orally) (reviewed in [4, 47]). All these studies were carried out in a low number of normal-weight patients, but most of them found a decrease in short-term food intake, while no significant effects were observed on hunger [4]. The decrease in food intake was very consistent, with a range of 11–29%, suggesting a clear role for opioid receptors in human feeding behavior. However, an important concern has been raised by the fact that some [48, 49], but not all [50], have shown that naltrexone caused nausea. About 19% of subjects reported nausea after the administration of naltrexone, compared to 9% receiving placebo [49, 51]. Although these studies failed to find a correlation between food intake reduction and nausea, further studies will be necessary to clearly elucidate if this side effect might contribute to the naltrexone-induced suppression in food intake. The actions of naloxone and naltrexone on feeding behavior have also been studied in obese patients. Both opioid receptor antagonists were able to suppress food intake, and some of those obese subjects reported also a decrease in hunger. However, nausea was also observed in several patients after drug administration [4, 52].

Although the effects of naltrexone on short-term food intake are clear, it fails to produce consistent weight loss, even at high doses (i.e. 300 mg/day) [53–55]. However, combination therapy with naltrexone and bupropion (an antidepressant that selectively binds to the
dopamine transporter) appears to be very efficient and is currently under phase III trial. Combined naltrexone/bupropion produces a synergistic increase in POMC neuron firing, a synergistic reduction in food intake in rodents, and greater weight loss in obese human subjects [56]. Several independent clinical studies have tested this combination during the last years. In one of these reports, 419 patients with uncomplicated obesity were treated with placebo or three doses of immediate-release naltrexone combined with 400 mg/day sustained-release bupropion for up to 48 weeks. In this phase II study on obese subjects, combination therapy resulted in significantly greater weight loss than placebo, naltrexone monotherapy, or bupropion monotherapy [56]. Another recent clinical study carried out a 56-week, randomized, placebo-controlled trial that examined the efficacy and safety of naltrexone plus bupropion as an adjunct to intensive behavior modification (BMOD). 793 obese participants were treated with either placebo plus BMOD, or sustained-release naltrexone (32 mg/day) combined with sustained-release bupropion (360 mg/day) plus BMOD. After 56 weeks, the combined naltrexone/bupropion treatment showed a higher reduction in body weight and an improvement in markers of cardiometabolic disease risk [57]. However, the treatment with these drugs was associated with more reports of nausea than that with placebo. To date, the clinical report with the largest population size was the Contrave Obesity Research I (COR-I) study, which assessed the effect of naltrexone/bupropion treatment on body weight in 1,742 overweight and obese participants [58]. These patients were distributed in a randomized, double-blind, placebo-controlled phase III trial undertaken at 34 sites in the USA. Participants were randomly assigned in a 1:1:1 ratio to receive sustained-release naltrexone (32 mg/day) plus sustained-release bupropion (360 mg/day), sustained-release naltrexone (16 mg/day) plus sustained-release bupropion (360 mg/day), or matching placebo twice a day, given orally for 56 weeks. Similarly to the previous studies, patients treated with the combination of naltrexone/bupropion showed a higher reduction in body weight [58]. However, yet again a significant percentage of the treated subjects (around 28%) reported nausea, compared to 5% of placebo-treated individuals. Headache, constipation, dizziness, vomiting, and dry mouth were also more frequent in the naltrexone plus bupropion groups than in the placebo group [58]. Taken together, these data indicate the need for further development and assessment of the opioid system as a drug target to overcome study design concerns including: use of nonselective opioid antagonists, failure to include a placebo-controlled group, use of relatively low number of subjects and/or non-inclusion of stratified patients such as binge obese patients.

### Genetic Manipulated Models for the Metabolic Study of the Opioid System

Pharmacological results have been strengthened using genetically manipulated mice. More specifically, the metabolic alterations in mice deficient in MOR and KOR have been studied using different diets. The first report studying the effects of MOR deficiency on energy balance dates from 2005 and found that MOR was not essential for the regulation of energy balance when the mice were fed on standard diet [59]. However, MOR-deficient mice were resistant to diet-induced obesity due to the higher expression of CPT-1 in the skeletal muscle, suggesting a stimulated fatty acid oxidation in comparison to wild-type mice [59]. In addition to this beneficial effect on body weight, the lack of MOR also improved glucose tolerance after high-fat diet [59]. Importantly, all these effects were independent of food intake since MOR-deficient mice show no alterations in feeding behavior. Similarly, an independent group has shown that MOR-deficient mice exposed to high caloric palatable diet gained less weight and fat mass compared to wild-type mice [60]. Moreover, the lack of MOR improved glucose tolerance when the mice were fed on this diet. In agreement with the
previous study, all these actions were independent of food intake. However, this work showed that MOR-deficient mice on standard diet gained more body weight and adiposity while eating more chow [60]. Finally, another report studied the effect of MOR deficiency on the motivational properties of food intake and the hedonic processing of feeding behavior [61]. These authors found that under a certain reinforcement schedule MOR-deficient mice showed a decreased motivation to eat both normal diet and sucrose pellets [61]. However, mice lacking MOR showed unaltered cognitive abilities, indicating that the endogenous MOR pathway mediates motivation to eat but is not essential for the hedonic properties of food [61].

On the other hand, it has been recently demonstrated that the genetic ablation of KOR in mice alters energy, glucose and lipid metabolism in response to a high-fat diet. KOR-deficient mice were resistant to weight gain even after prolonged exposure to a high-fat diet, and this was driven by maintenance of energy expenditure and locomotor activity levels [62]. Furthermore, mice lacking KOR and fed on a high-fat diet had reduced hepatic fat storage due to a reduction in triglyceride formation and an increase in fatty acid β-oxidation in the liver [62]. Overall, it can be concluded that gross changes in body weight are absent in both KOR-deficient mice and also in combinatorial mutant mice lacking all three opioid receptors, MOR, DOR and KOR, when fed a standard low-fat chow diet. However, in conditions of prolonged consumption of high-fat diets, opioid receptor antagonists might be useful in reducing the metabolic damage caused by diet-induced obesity.

In addition to the effects of KOR deficiency, the metabolic alterations caused by the lack of dynorphin, an endogenous ligand of the KOR, have also been taken in consideration. Contrary to KOR-deficient mice, mice with genetic ablation of dynorphin did not show any change in body weight when fed on high-fat diet [63]. However, serum levels of free fatty acids were decreased in dynorphin-deficient mice fed on a high-fat diet, indicating a decreased fatty acid output into the circulation or increased fatty acid oxidation [63]. Although the tissues where changes in fatty acid oxidation can be altered have not been studied, overall, it can be hypothesized that the endogenous dynorphin-KOR pathway plays an important role in the modulation of fatty acid metabolism. The most relevant findings in mice with a disruption of dynorphin were observed during fasting. As a matter of fact, the lack of dynorphin reduces fat mass and body weight during a 24-hour fast [63]. These effects were not caused by alterations in energy expenditure or locomotor activity, but by the increased activity of the sympathetic nervous system. Moreover, it was found that males, but not females, deficient in dynorphin have a reduced respiratory exchange ratio, indicating a state where lipid mobilization is favored [63]. It is important to note that there are no studies available in the literature regarding the response of KOR-deficient mice to fasting, but taking into account that KOR antagonists reduce the fasting-induced hyperphagia in rats [64] and that KOR mutant mice also show alterations in fatty acid metabolism, it seems plausible to hypothesize that mice lacking the KOR might respond similarly as dynorphin-deficient mice.

**Concluding Remarks**

The importance of the endogenous opioid system modulating feeding behavior and other parameters that are crucial for the regulation of energy balance has been conclusively demonstrated by numerous preclinical and clinical reports (summarized in fig. 1). However, there are still some important gaps in our knowledge surrounding several opioid-related issues. For instance, it seems clear that the complete lack of MOR and KOR causes important alterations in energy balance, particularly when mice are fed on fat-enriched diets. However,
the potential role of DOR deficiency has not been studied, and according to pharmacological data, it might be possible to find some important metabolic alterations after the disruption of DOR. It should be also emphasized that, despite the large amount of data gleaned over the last few years regarding the involvement of opioid receptors as key players in food/alcohol reward, there are strong concerns as to the extent to which the outcome of studies with opiate antagonists can be interpreted as evidence for a direct role of opioids or whether these are a consequence of the side effects associated with administration of these drugs. Although the balance of evidence suggests that behavioral effects of opioid antagonists have been demonstrated independently of side effects, further studies with specific genetic ablation of the different opioid receptors at specific neuronal clusters (nuclei) should be carried out in experimental animals in comparison with standard pharmacological approaches to ensure that the data generated can be interpreted correctly. Of particular relevance are the location of opioid receptors in several areas of the mesolimbic dopamine system such as the ventral tegmental area and the nucleus accumbens. It will be of great interest to generate and characterize mice lacking MOR, KOR or DOR in these specific brain areas in order to understand more precisely the molecular underpinnings modulating the actions of the endogenous opioid system on the hedonic properties of food. Also, the issue of gender should be taken into consideration since it is known that KOR agonists in males elicited greater suppression of food intake than in females. Similarly, in humans mixed KOR/MOR ligands have been found to produce greater analgesia in women than in men. In contrast, in animals, selective KOR agonists have been found to produce greater antinociceptive effects in males than in females. Collectively, the studies indicate the existence of marked gender- and species- differences in opioid receptor mediated biological effects [65].

Finally, clinical data reinforce the results obtained in laboratory animals, indicating that the blockade of opioid receptors diminishes food intake in both lean and obese patients. More importantly, very recent findings have shown that the combination of naltrexone and bupropion has the ability to induce weight loss in obese patients. This approach, which is already in a phase III trial, has raised new hopes for the treatment of obesity. Indeed, the main problem that is foreseen relates to the side effects found in a percentage of those patients who reported nausea together with other more infrequent discomforts. This highlights the need for the development of new compounds, e.g. inverse agonists, able to achieve therapeutic efficacy at lower receptor occupancies, which should lead to a better safety and tolerability profile. Although additional studies are needed to clarify the importance of these undesirable effects during the development of the therapy, it might be important to analyze if this treatment should be only advised in certain obese patients, but not in others with particular clinical history.

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Disclosure Statement

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