Cannabinoids and Feeding:
The Role
of the Endogenous Cannabinoid System
as a Trigger for Newborn Suckling

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SUMMARY. Cannabinoids are known to enhance appetite by activating cannabinoid (CB_1) receptors. This phenomenon is exploited to combat cachexia and loss of appetite in cancer and AIDS patients. The endocannabinoid 2-arachidonylglycerol (2-AG) is present in milk. Evidence is presented supporting a critical role for CB_1 receptors in survival of mouse pups. Thus neonates do not gain weight and die within the first week of life when their receptors are blocked. This is due apparently, to an inability to ingest maternal milk. This suggests that the endocannabinoid-CB_1 receptor system is unique in its absolute control over the initiation of the neonatal milk suckling response. It is further proposed that cannabis-based medicines should be developed to benefit infant failure to thrive. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc. com> Website: <http://www.HaworthPress.com> 2002 by The Haworth Press, Inc. All rights reserved.]*

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ABBREVIATIONS. CB_1, cannabinoid 1, 2-AG, 2-arachidonylglycerol, CBD, cannabidiol

Cannabis is well known appetite stimulant (Abel 1971; Mattes et al. 1994; Fride 2002a). It is possible that the enhancement of appetite is selective for snack foods (Foltin, Brady, and Fischman 1986; Mattes, Shaw, and Engelman 1994). A role of the endocannabinoid system in the primitive invertebrate, *Hydra vulgaris*, has been demonstrated (De Petrocellis et al. 1999), thus pointing at a very widespread stimulatory role for cannabinoids in feeding. This, for most cannabis users, undesirable "side effect," has been clinically utilized for a number of years to combat a reduction in appetite and consequent weight reduction and wasting, as seen in conditions including AIDS and cancer (Mechoulam, Hanus, and Fride 1998). However, few controlled clinical studies have been performed (Bennett and Bennett 1999). In open pilot studies, dronabinol (Δ^9-THC) caused weight gain in the majority of subjects (Plasse et al. 1991). A relatively low dose of dronabinol, 2.5 mg twice daily, enhanced appetite and stabilized body weight in AIDS patients suffering from anorexia (Beal et al. 1997) for at least 7 months. In another study on AIDS patients, no weight gain was reported over the course of 12 weeks of dronabinol administration (2.5 mg twice a day), whereas a dose of 750 mg/day of megestrol acetate (a synthetic progestational drug), effected significant weight gain (Timpone et al. 1999). In that study, a high dose of megestrol (with potential adverse effects including dyspnea and hypertension), and a low dose of dronabinol were used. Higher doses of dronabinol may be more effective, although side effects such as weakness, confusion, memory impairment and anxiety, are a concern.

When dronabinol was administered to healthy volunteers, an increase in caloric intake was recorded after twice daily administrations for 3 days, when rectal suppositories were used, rather than the oral route (Mattes et al. 1994). When the effects of cannabis smoking by healthy volunteers on the intake of various types of food were compared, a selective increase in snack foods was observed (Foltin, Brady, and Fischman 1986). Thus the use of higher doses of cannabinoids as well as different routes of administration including the rectal (Bennett and Bennett 1999) or the sublingual (Whittle, Guy, and Robson 2001) route, should be further investigated.

Studies in laboratory animals have confirmed the human data, and unequivocally shown that cannabinoid 1 (CB_1) receptors mediate cannabinoid-induced increase in food ingestion (Williams and Kirkham 2002), especially of palatable

foods (Koch and Matthews 2001). Thus both exogenous cannabinoids (Δ^9-THC) and the endocannabinoid anandamide-induced enhancement of appetite were reversed by the specific CB_1 antagonist SR141716A (Williams, Rogers, and Kirkham 1998; Williams and Kirkham 2002). SR141716A injected by itself reduced appetite and body weight. Whether palatability is required for the antagonist's anorectic effect is controversial (Colombo et al. 1998; Freedland, Poston, and Porrino 2000; Arnone et al. 1997). In a chronic study in mice, very low doses of anandamide (0.001 mg/kg) were effective in enhancing food intake (Hao et al. 2000), in according with a stimulatory effect of very low doses of anandamide in a series of cannabimimetic assays (Sulcova, Mechoulam, and Fride 1998).

INTERACTIONS OF THE ENDOCANNABINOID SYSTEM WITH HORMONES REGULATING FOOD INTAKE

CB_1 receptors have been located in the hypothalamus (Herkenham et al. 1991; Mailleux and Vanderhaeghen 1992), a brain structure which is important in weight regulation. Although the precise mechanism by which cannabinoid receptors enhance appetite and food intake is not known, progress has been made in recent years to uncover such mechanisms (Mechoulam and Fride 2001). Thus Arnone et al. (1997) showed that the neuropeptide Y (NPY)-induced increase in sucrose drinking was inhibited by SR141716A, possibly linking this hormone, which is known to enhance food intake (Mechoulam and Fride 2001), to cannabinoid-stimulated appetite.

The hormone leptin is produced by fat tissue and is considered to be a key signal through which the hypothalamus senses the nutritional state of the body and helps maintain weight within a narrow range (Friedman 2000; Schwartz et al. 2000).

Within the hypothalamus, the arcuate nucleus contains neurons with receptors for two appetite-stimulating peptides (neuropeptide Y and agouti-related protein), as well as receptors for two peptides that reduce appetite (α-melanocyte-stimulating hormone and cocaine-and-amphetamine-regulated transcript). Leptin directly suppresses the activity of the two appetite-stimulating peptides, and stimulates the activity of the appetite-reducing ones, thereby decreasing appetite. Other molecules indirectly affected by leptin include melanin-concentrating hormone and a family of neuropeptides called orexins, which enhance appetite, as well as corticotropin-releasing hormone and oxytocin, which cause mice to eat less and to lose weight.

Di Marzo et al. (2001) have demonstrated that the endocannabinoid receptor system is an additional factor in this already complex weight-regulating system. Thus, when they administered leptin, the levels of the endocannabinoids anandamide and 2-arachidonylglycerol in the hypothalamus of normal rats were

reduced. Further evidence strengthens the idea that leptin down-regulates endocannabinoids. In a strain of obese rats in which leptin activity is impaired, the levels of endocannabinoids are higher than normal (Di Marzo et al. 2001). The same is true of obese *ob/ob* mice, which have an inherited lack of leptin, and of obese *db/db* mice, which have defective leptin receptors. Endocannabinoid levels are not affected in the cerebellum (which is commonly associated with motor coordination, but not with feeding) in these mice.

Taking together the human and animal studies, the effects of the cannabinoid system on food intake and appetite are significant, representing one of a multitude of players involved in this vital function.

ENDOCANNABINOIDS IN FOOD SUBSTANCES

The discovery of anandamide in chocolate (di Tomaso, Beltramo, and Piomelli 1996) raised the possibility that endocannabinoids contribute to the attractiveness of, and perhaps the intense craving for, this desirable food. Indeed, orally administered endocannabinoids (anandamide and 2-AG), albeit in very high doses, induced cannabimimetic effects in mice (Di Marzo et al. 1998). The very low amounts of anandamide found in cocoa powder and even lower concentrations in unfermented cocoa beans, would suggest the possibility that the anandamide in chocolate may be an artifact of processing (Di Marzo et al. 1998). Anandamide congeners that do not bind CB_1 receptors, including linoleoyl ethanolamide, oleoyl ethanolamide and oleamide ("sleep factor," Cravatt et al. 1995), all display cannabiminetic effects when applied *in vivo* (Fride at al. 1997), probably by inhibiting the fatty acid amide hydrolase (FAAH) enzyme which breaks down anandamide (see Fride 2002a). Oleamide, when given orally, displayed cannabimimetic effects in mice at doses several magnitudes higher than those present in chocolate, similar to orally administered anandamide (Di Marzo et al. 1998). Taken together, these results suggest that anandamide in chocolate, whether present in cocoa beans, or as an artifact of processing, could be responsible for any cannabinoid contribution to "chocolate craving." Future studies, testing anandamide and its congeners in more subtle behavioral assays such as "drug discrimination" or "place preference" designs may shed further light on the putative role for endocannabinoids in the rewarding effects of chocolate.

Interestingly, in the same study, and in a more recent one, relatively high concentrations of the endocannabinoid 2-AG but very low quantities of anandamide were detected in various types of milk (for instance, 8.7 ± 2.8 μg 2-AG/g extracted lipids from "mature" human milk). These concentrations of 2-AG were much higher than those found in other foods such as soybeans, hazelnuts and oatmeal (Di Marzo et al. 1998; Fride et al. 2001a).

DEVELOPMENTAL ASPECTS
OF THE ENDOCANNABINOID-CB_1 RECEPTOR SYSTEM

Based on the findings described above, it is suggested that, as 2-AG is found in milk in significant amounts, this endocannabinoid must be of importance for the development of the newborn mammal. Several observations on developmental aspects of the endocannabinoid system in the central nervous system support such a hypothesis.

First, "atypical distribution patterns" of CB_1 receptors (i.e., a transient presence during development in regions where none are found at adulthood) were detected in white matter regions including the corpus callosum and anterior commissure (connecting neuronal pathways between the left and right hemispheres) between gestational day 21 and postnatal day 5, suggesting a role for endocannabinoids in brain development (Romero et al. 1997).

Further, although initial reports studying the development of the cannabinoid receptor system during the first weeks of postnatal life in the rat described a gradual increase in brain CB_1 receptor mRNA (McLaughlin and Abood 1993) and in the density of CB_1 receptors (Belue et al. 1995; Rodriguez de Fonseca et al. 1993), in later studies CB_1 receptor mRNA was also detected from gestational day 11 in the rat (Buckley et al. 1998). Additional studies have uncovered more complex developmental patterns. Thus, whereas the highest levels of mRNA expression of the CB_1 receptor are seen at adulthood in regions such as the caudate-putamen and the cerebellum, other areas such as the cerebral cortex, the hippocampus and the ventromedial hypothalamus display the highest mRNA CB_1 receptor levels on the first postnatal day (Berrendero et al. 1999; Fernandez-Ruiz et al. 2000). Finally, endocannabinoids were also detected from the gestational period in rodents, 2-AG at 1000 fold higher concentrations than anandamide. Interestingly, while anandamide displayed a gradual increase, constant levels of 2-AG were measured throughout development except for a single a peak on the first postnatal day (Berrendero et al. 1999).

Is it possible therefore, that the high levels of CB_1 receptor mRNA and 2-AG which have been observed on the first day of life in structures including the hypothalamic ventromedial nucleus (which is associated with feeding behavior) comprise a major stimulus for the first episode of milk suckling in the newborn?

BLOCKADE OF CB_1 RECEPTORS IN NEWBORN MICE

Over the last few years, our group has investigated a role for the endocannabinoid system immediately after birth in mice. Administration of the specific CB_1 receptor antagonist SR141716A to the nursing mother had no effect on maternal weight, pup growth and development, or on maternal behavior (Fride,

Ginzburg and Mechoulam, unpublished observations). However, when CB_1 receptors were blocked by SR141716A in one day old pups by a single sc injection of SR141716A, a complete growth arrest and death within the first week of life was observed in virtually all SR141716A-treated pups (Fride et al. 2001a; Figure 1).

This devastating effect of SR141716A on the pups was dose-dependent (between 5-20 mg/kg). Furthermore, for the complete (almost 100% mortality) effect to take place, the antagonist had to be injected within the first 24 hours of life. Co-administration of Δ^9-THC almost completely reversed the effect, thus strongly suggesting that the SR141716A-induced effects were CB_1 receptor mediated. Co-administration of the endocannabinoid 2-AG did not reverse the SR141716A-induced mortality, presumably due to its rapid breakdown. However, 2-AG injected together with its "entourage" (fatty acid-esters which are always co-released with 2-AG, but which do not bind CB_1 receptors, and which counteract the breakdown and reuptake of 2-AG; see Ben-Shabat et al. 1998), significantly antagonized the growth-arresting effects of SR141716A on the pups (Figure 2). Subsequent experiments designed to further support the specificity of the CB_1 receptor in the mediation of the antagonist-induced pup mortality indi-

FIGURE 1. Five day old vehicle-injected (left) and SR141716A-injected (right) mouse pups. Pups, from the same litter, were injected sc (10 μl/g) within 24 hr after birth with vehicle (ethanol:emulphor:saline = 1:1:18), or SR141716A (20 mg/kg).
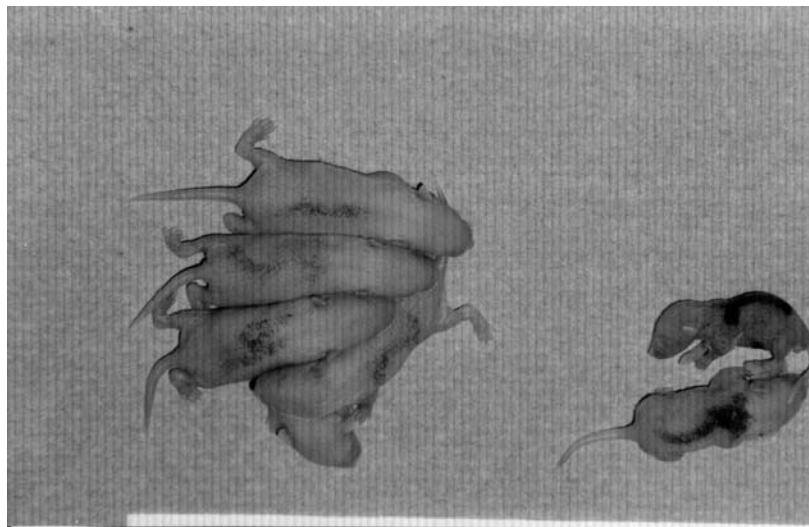
cated that cannabidiol (CBD), the non-psychoactive, non-CB_1 receptor binding cannabinoid, did not reverse the effects of SR141716A (Fride et al. 2001a; Figure 2), while the CB_2 receptor antagonist, SR144528, did not affect pup growth (unpublished observations).

MECHANISMS OF THE CB_1 RECEPTOR BLOCKADE-INDUCED GROWTH STUNTING EFFECTS

An initial investigation of possible mechanisms involved in sequelae of CB_1 receptor blockade in pups suggested that maternal behavior toward SR141716A-injected pups was not adversely affected. On the contrary, the dams spent significantly more time "licking" and nursing the antagonist-treated pups (Fride et al. 2001a). Rather, the CB_1 receptor blockade on day 1 of life disables the ability of the newborns to initiate milk suckling, as their stomachs were empty of milk (Fride et al. 2001a).

FIGURE 2. Summary of survival rates in pups one week after birth after various treatments on day 1 of life. SR1 = SR141716A (20 mg/kg), SR2 = SR144528 (20 mg/kg), CBD = cannabidiol (20 mg/kg), Entourage = palmityl glycerol (5 mg/kg) and lineoyl glycerol (10 mg/kg); these were added to the injection of 2-AG (1 mg/kg). LPA = lysophosphatidic acid (18:1, n-9, 20 mg/kg). All compounds were injected sc in the neck or flank in volumes of 10 μl/g.
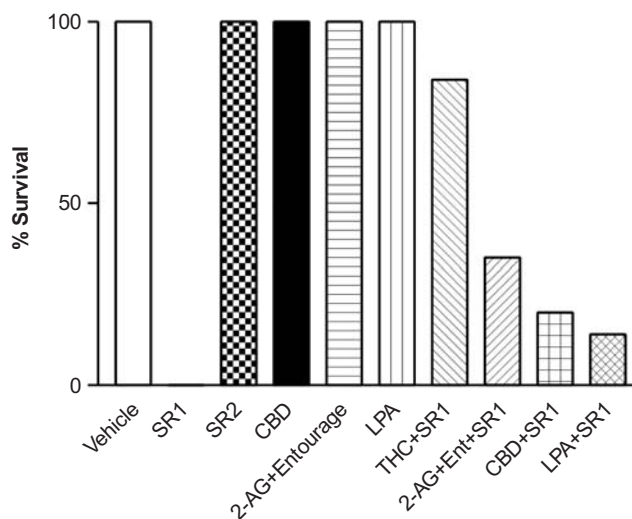
More recent evidence for the role of CB_1 receptors in milk suckling is derived from CB_1 receptor-deficient ($CB_1^{-/-}$ knockout) mice, where it was observed that the CB_1 receptor antagonist had significantly less severe effects on the $CB_1^{-/-}$ pups, as compared to the effects on wild type mice (Fride et al., in preparation).

Lysophosphatidic acid (LPA) is a multifunctional lipid mediator with growth factor-like properties. LPA occurs in brain in considerable concentrations and is structurally similar to the endocannabinoid 2-AG. The LPA and CB_1 receptors display substantial (30%) homology. LPA, with 2-arachidonic acid as the acyl moiety, differs only by the absence of a phosphate group from 2-AG while a related lysophosphatidic acid (with 1-arachidonic acid as the acyl moiety) has been detected in rat brain (Sugiura et al. 1999). A defective suckling response was reported in neonatal mice that have a targeted deletion of the gene for the LPA receptor (lp_{A1}) (Contos et al. 2000). Our group therefore investigated the possibility that LPA and 2-AG may interact at their receptors. If the inhibition of milk ingestion in our experiments were due to an interaction of the CB_1 antagonist at the LPA receptor, or alternatively, if LPA interacts with the CB_1 receptor, then co-application of LPA with SR141716A on newborn pups should reverse the antagonist inhibition of pup development. This was not the case in our experiments. Thus, when LPA was co-injected with SR141716A, only a temporary delay in mortality, with borderline significance ($p = 0.09$), was observed (Fride, Rosenberg, and Mechoulam 2001b). Moreover, LPA did not bind to CB_1 receptors (Hanus and Fride, unpublished observations). Since the LPA employed contained oleic acid as the acyl moiety, and not arachidonic acid (which can not be obtained commercially), further investigation of the interaction between the LPA and CB_1 receptor systems is warranted.

Several neuroactive substances have been implicated in milk suckling. For example, Smotherman and colleagues (Petrov, Varlinskaya, and Smotherman 1998) have demonstrated an inhibition of several components of the suckling response after injection of naloxone into the cerebral ventricles of rat pups. When effects of intracisternal injections of a specific μ opiate receptor antagonist on weight gain were recorded, only a slight, transient reduction was seen; similar injections into the cerebral ventricles did not have any effect on body weight (Petrov et al. 1998).

Taken together, our studies argue for a critical role for CB_1 receptor activation in milk suckling in the newborn, presumably by 2-AG produced by the neonatal brain. As far as is known, the endocannabinoid-CB_1 receptor system is the first neural system discovered thus far that seems to display complete control over milk ingestion and neonatal survival.

CONCLUSIONS

Our data have indicated that the CB_1 receptor antagonist had to be injected within 24 hr after birth of mouse pups in order to produce a virtual 100% mortality effect (injection on day 2 resulted in less than 50% mortality). It is proposed that without CB_1 receptor activation by 2-AG (or another as yet undefined endocannabinoid) within the first 24 hr of life, the first suckling episode is not initiated. As the pups have not suckled yet, the source of this 2-AG must be the pup's brain, and not maternal milk. This is compatible with the surge of 2-AG and CB_1 receptor mRNA in the 1-day old rat brain (Berrendero et al. 1999; Fernandez-Ruiz et al. 2000). The lower levels of 2-AG and CB_1 receptors present from day 2 onward are apparently too low, or too late, to allow the suckling response to be initiated on subsequent days.

These observations further suggest that the enhancement in appetite and food intake induced by cannabinoids in the adult organism may only be the tip of the iceberg of the vital role for the cannabinoid system in milk suckling immediately after birth (Fride et al. 2001a). The comparatively more partial control of the endocannabinoid system of appetite and food intake by the mature organism should not diminish our efforts to develop cannabis-based medicines for appetite stimulation in conditions involving cachexia. Rather, it does suggest that treatment of children suffering such conditions may benefit at least as much as adults from cannabinoids to combat anorexia (Fride 2002b). Further, treating infants suffering from a failure to thrive with cannabinoid-derived medicines deserves future research.

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