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Dopamine affects the in vitro basal secretion of rat placenta opioids in an opioid and dopamine receptor type-specific manner

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Abstract

Opioid peptides and their receptors are present in the placenta of many species. Dopamine plays an important role in the regulation of opioid release in the nervous system and it may play a similar role in placenta since dopamine receptors are also present in this tissue. The aim of the present work was to examine the effect of dopamine on the basal release of rat placental opioids. The effect of several dopamine receptor agonists and antagonists was tested on the release of immunoreactive β-endorphin and immunoreactive dynorphin from perfused rat placenta fragments. We found that dopamine and apomorphine stimulated the secretion of immunoreactive β-endorphin in a dose-dependent manner. The selective D_1 dopamine receptor agonist (±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride or SKF-38393 reproduced the effect of dopamine while the selective D_1 dopamine receptor antagonist *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl 1,2,3,4,5-tetrahydro-1*H*-benzazepine hydrochloride or SCH-23390, prevented the dopamine- and SKF-38393-induced increase of immunoreactive β-endorphin secretion. The selective and potent D_2 dopamine receptor agonist (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxytetralin hydrochloride or PPHT had no effect on immunoreactive β-endorphin. Finally, none of the agonists tested had any effect on the in vitro secretion of placental immunoreactive dynorphin. Our results suggest that dopamine affects the basal release of placental opioids in an opioid and dopamine receptor-specific manner, its effect being different from the effect it exerts on β-endorphin in the rat neurointermediate pituitary lobe.

Keywords: Dopamine; Placenta; β-Endorphin; Dynorphin; Perfusion; (Rat)

1. Introduction

It is now well established that the placentae of many species produce opioids and contain opioid receptors, findings suggesting that placental opioids may exert local effects (Nakai et al., 1978; Liotta and Krieger, 1980; Liotta et al., 1982; Krieger, 1982; Lemaire et al., 1983; Weindl et al., 1983; Valette et al., 1980; Ahmed and Horst, 1986; Chen et al., 1986; Hon and Ng, 1986; Laatikainen et al., 1987; Margioris et al., 1988; Facchinetti et al., 1990; Davies et al., 1991; Zhang et al., 1991; Cemerikic et al., 1992). However, the regulation of placental opioid synthesis and secretion as well as the possible physiological role of these opioids remains obscure.

Dopamine affects proopioimelanocortin in hypothalamus (Matera and Wardlaw, 1993), anterior pituitary (Sweep et al., 1990) and neurointermediate pituitary lobe (Young et al., 1993). The effect of dopamine on proopiomelanocortin appears to be tissue-specific since in the neurointermediate pituitary lobe the secretion of the proopiomelanocortin opioid product β-endorphin is inhibited by D_2 dopamine receptor agonists (Autelitano et al., 1985 and Autelitano et al., 1987; Farah and Mueller, 1989) while in the anterior pituitary it is stimulated by the D_2 dopamine receptor agonist LY-141865 (Farah and Mueller, 1989). Dopamine also affects neuronal dynorphin. Its effect appears to be site- and dopamine receptor-specific. Indeed, the D_1 dopamine receptor agonist SKF-38393 increases the striatonigral dynorphin-A while the D_2 dopamine receptor agonist quinpirole was found to be ineffective (Trujillo et al., 1990; You et al., 1994).

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Placenta is a tissue with no innervation. However, high levels of dopamine are detectable in the amniotic cavity. Indeed, dopamine is easily detectable in both the decidua and amniotic fluid (Tada et al., 1991). Its levels rise significantly towards term, suggesting that its function may involve regulation of fetal maturation and/or mechanism(s) of labor and delivery. The latter is in accord with the fact that dopamine stimulates the decidual production of prostaglandin F_{2a} (Tada et al., 1991). Furthermore, the placental brush-border actively transports dopamine against a concentration gradient (Ramamoorthy et al., 1992). Human placenta also contains D_1 and D_2 dopamine receptors (Petit et al., 1990). Furthermore, it has been shown that dopamine inhibits the secretion of human placental lactogen via a D_2 dopamine receptor (Petit et al., 1990, 1993) and that D_2 dopamine receptor agonists reduce the activity of cAMP and inhibit calcium influx in human placenta (Vaillancourt et al., 1994b). In addition, placental production of progesterone appears to be stimulated by dopamine (Battista et al., 1990). Furthermore, the D_1 dopamine receptor agonist SCH-23390 elicits a dose-dependent stimulation of cAMP formation in human term placenta (Ferre, 1986). Thus, both D_1 and D_2 types of dopamine receptors appear to be functional in human and rodent placenta.

The aim of the present work was to test if dopamine affects the basal secretion of placental opioids. For this purpose we utilized an in vitro perfusion system of rat placenta at term, which we have previously used successfully (Margioris et al., 1990a). The slices were exposed to several dopamine receptor agonists and antagonists and their effect on the basal release of immunoreactive β-endorphin and immunoreactive dynorphin was measured and compared to pre-exposure levels.

2. Materials and methods

2.1. Tissue preparation and perfusion

Pregnant Sprague-Dawley rats were killed on the 20th day of pregnancy. Their placentae were rapidly dissected, cut in pieces of few mm thickness, washed in PBS, and packed in the perfusion chambers. The perfusion medium consisted of Dulbecco's Modified Eagles Medium (Gibco, New York,, NY, USA) supplemented with 0.1% defatted human serum albumin (Sigma, St. Louis, MO, USA), 0.2% glucose, 100 kallikrein units/ml aprotinin, 100 U/ml penicillin, 0.1 mg/ml streptomycin and 25 mg/ml amphotericin (Sigma), maintained throughout the experiment at 37°C in an atmosphere of 95% O_2-5% CO_2. A total of 700 mg of placental fragments was packed inside each perfusion chamber between two layers of Sephadex-50 gel (Pharmacia, Piscataway, NJ, USA) preswollen overnight in the perfusion medium. Each perfusion chamber (Endotronics, Forma Scientific, Marietta, OH, USA) consisted of a cap, metallic grid, glass fiber filter, a layer of swollen Sephadex gel, placental fragments, a second layer of Sephadex gel, filter, metallic grid and cap, as previously described (Margioris et al., 1988, 1990a). All chambers were positioned vertically inside a recirculating water bath; the medium was pumped upwards (countergravity) by 3-channel peristaltic pumps (Pharmacia). A 3-way valve was placed in between each chamber and the medium reservoir. The flow rate was gradually raised to 0.3 ml/min within 15 min following the beginning of each perfusion and was kept constant thereafter. The perfusion media and all test materials were maintained at 37°C in an atmosphere of 95% O_2/5% CO_2 throughout the experiment. Five-minute fractions were collected. The first 90 min of perfusion were considered as equilibration period and were not assayed. Following this period, the release of immunoreactive β-endorphin and immunoreactive dynorphin in the perfusion medium was stable for five additional hours. The KCl-induced depolarization at the end of each experiment was used to evaluate the reserve secretory capacity of the perfused tissues. It usually caused a highly significant stimulation of immunoreactive β-endorphin and immunoreactive dynorphin release. A typical mean increase of immunoreactive β-endorphin following KCl-induced depolarization was five to six times that of basal levels, while that of immunoreactive dynorphin, four to five times.

2.2. Test protocols

The perfused tissues were exposed to the test substances for 5 min, i.e., a time period equal to the duration of a single perfusion fraction. 'Basal release' was defined as the mean concentration of three consecutive fractions immediately prior to each test pulse and 'stimulated release' as the mean concentration of the three main fractions comprising the response peak. The perfusion fraction collected during exposure of the tissue to the test substances was counted as the zero post-exposure fraction and was not used in the calculations for purely perfusion equilibration reasons (Margioris et al., 1988). To evaluate the effect of each test substance on the release of the two opioid peptides, the combined data of six different perfusions were used.

Dopamine, apomorphine (a D_2 and a weaker D_1 dopamine receptor agonist), the selective D_1 dopamine receptor agonist (±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol hydrochloride or SKF-38393, the selective D_1 dopamine receptor antagonist *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-1,2,3,4,5-tetrahydro-1*H*-benzazepine hydrochloride or SCH-23390, and the potent D_2 dopamine receptor agonist (±)-2-(*N*-phenylethyl-*N*-propyl)amino-5-hydroxytetralin hydrochloride or PPHT were purchased from RBI, Research Biochemicals International (Natick, MA, USA). The selection of the dopamine agonists and antagonist was based on papers describing the types of dopamine receptors in placenta (Onali et al., 1984;

Ferre, 1986; Petit et al., 1990, 1993; Vaillancourt et al., 1994b; Ogawa, 1995).

2.3. Radioimmunoassays

For the β-endorphin radioimmunoassay we used the 'EP-2' antiserum which was developed against synthetic rat β-endorphin (Margioris et al., 1988). It exhibits 100% cross reactivity with β-lipotropin. It does not recognize dynorphin A, dynorphin-(1–13), dynorphin-(1–8), [Met^5]enkephalin, or [Leu^5]enkephalin. The sensitivity of the assay was 2 pg/tube. Fifty percent displacement of the tracer was observed at 20 pg/tube. The tracer was an High-Performance Liquid Chromatography-purified [^{125}I]β-endorphin (Amersham, Arlington Heigths, IL, USA) and the standard synthetic rat β-endorphin (Peninsula, CA, USA). For the dynorphin radioimmunoassay, the 'D-2708' antiserum was used as previously described (Margioris et al., 1990b). This antiserum has been raised against synthetic porcine dynorphin-(1–13), which is identical to rat dynorphin-(1–13). It exhibits 100% cross reactivity with rat dynorphin-A, 30% cross reactivity with dynorphin-(1–8), and no cross reactivity with synthetic rat β-endorphin, γ-endorphin, α-neo-endorphin, [Met^5]enkephalin, or [Leu^5]enkephalin.

2.4. Statistical analysis

The effect of each test pulse was compared to basal secretion defined as the mean concentration of the three consecutive fractions immediately prior to each test pulse and to control pulses containing the test substance vehicles. Stimulated secretion was defined as the mean concentration of three main fractions comprising the response peak. Subsequently, the means of the basal secretions from six perfusions were grouped and compared to the grouped means of the stimulated values. The tests used were the *t*-test and Analysis of Variance (ANOVA). Following statistical evaluation, the data were converted to percentages for graphic representation. Statistical analysis of percentage differences was not done.

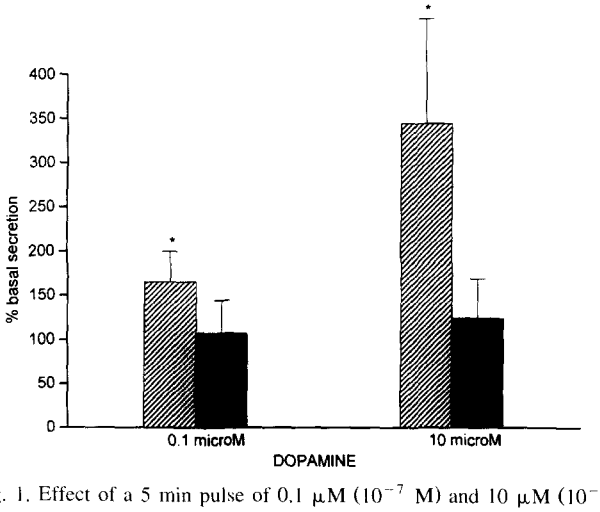

Fig. 1. Effect of a 5 min pulse of 0.1 μM (10^{-7} M) and 10 μM (10^{-5} M) of dopamine on the basal release of IR-β-endorphin (hatched bars) and IR-dynorphin (light gray bars). The bars represent the pooled data for six different perfusions. During each perfusion, 'basal release' was defined as the mean concentration of three consecutive fractions immediately prior to each test pulse and 'stimulated release' as the mean concentration of three main fractions comprising the response peak. The combined data were expressed as the percentage change of the group means for the six perfusions. * Statistical significance; the precise value of each *P* is mentioned in the text.

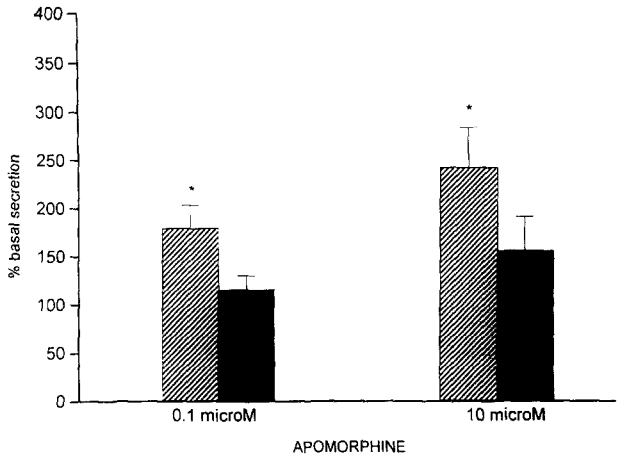

Fig. 2. Effect of a 5 min pulse of 0.1 μM (10^{-7} M) and 10 μM (10^{-5} M) of apomorphine on the release of IR-β-endorphin (hatched bars) and IR-dynorphin (light gray bars). The data were calculated as for Fig. 1.

3. Results

3.1. Effect of dopamine and apomorphine on the release of placental immunoreactive β-endorphin and immunoreactive dynorphin

Dopamine exhibited a stimulatory effect on placental immunoreactive β-endorphin release. Thus, at a concentra-

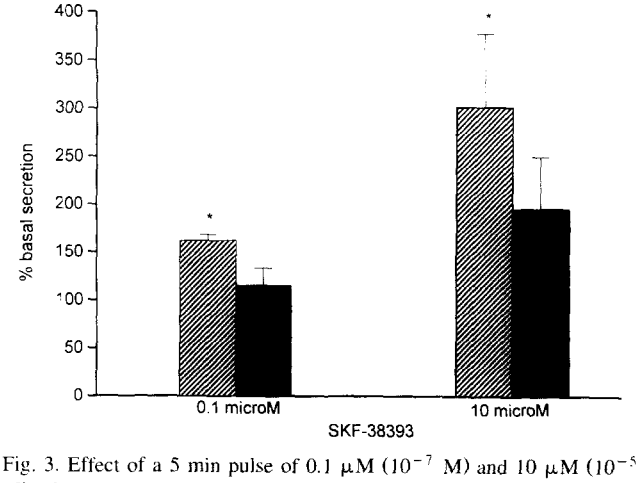

Fig. 3. Effect of a 5 min pulse of 0.1 μM (10^{-7} M) and 10 μM (10^{-5} M) of the selective dopamine D_1 receptor agonist SKF-38393 on the release of IR-β-endorphin (hatched bars) and IR-dynorphin (light gray bars). The data were calculated as for Fig. 1.

tion of 10^{-7} M dopamine increased the concentration of immunoreactive β-endorphin in the perfusion medium by 165 ± 35% (mean ± S.E.) compared to basal levels ($n = 6$, $P < 0.01$) (see Materials and methods) while at 10^{-5} M it increased immunoreactive β-endorphin by 344 ± 118% ($n = 6$, $P < 0.05$) (Fig. 1). Apomorphine had a similar stimulatory effect. Indeed, at a concentration of 10^{-7} M it increased the concentration of immunoreactive β-endorphin in the perfusion medium by 179 ± 24% ($n = 6$, $P < 0.05$) and at 10^{-5} M by 241 ± 42% ($n = 6$, $P < 0.01$) (Fig. 2). Dopamine and apomorphine did not have any statistically significant effect on the release of placental immunoreactive dynorphin (Fig. 1 and Fig. 2).

3.2. Effect of the selective D_1 dopamine receptor agonist SKF-38393, the selective D_1 dopamine receptor antagonist SCH-23390, and of the potent and selective D_2 dopamine receptor agonist PPHT on the secretion of placental immunoreactive β-endorphin and immunoreactive dynorphin

The selective D_1 dopamine receptor agonist SKF-38393 stimulated the release of immunoreactive β-endorphin in a highly significant manner. Thus, at a concentration of 10^{-7} M SKF-38393 increased immunoreactive β-endorphin by 160 ± 7%, $n = 6$ ($P < 0.001$), and at 10^{-5} M by 300 ± 7%, $n = 6$ ($P < 0.001$) (Fig. 3). To evaluate the significance of the D_1 dopamine receptor-mediated effect on immunoreactive β-endorphin secretion the selective D_1 dopamine receptor antagonist SCH-23390 was used. A continuous 5-h exposure of the tissue to 10^{-5} M of SCH-23390 had no effect on either basal or KCl-induced release of immunoreactive β-endorphin or immunoreactive dynorphin. The presence of SCH-23390, however, completely abolished both the dopamine- and the SKF-38393-mediated increase of immunoreactive β-endorphin, suggesting that most if not all of the effect of dopamine was mediated by the D_1 dopamine receptor (data not shown).

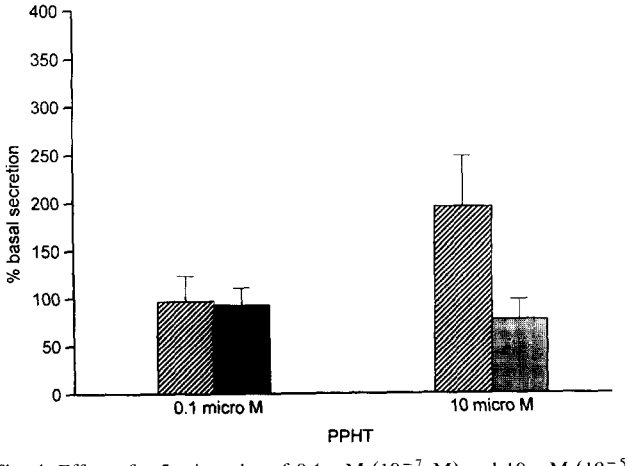

Fig. 4. Effect of a 5 min pulse of 0.1 μM (10^{-7} M) and 10 μM (10^{-5} M) of the selective dopamine D_2 receptor agonist PPHT on the release of IR-β-endorphin (hatched bars) and IR-dynorphin (light gray bars). The data were calculated as for Fig. 1.

SKF-38393 did not have any effect on immunoreactive dynorphin although at 10^{-5} M it did cause a slight but statistically non-significant increase (Fig. 3). Fig. 4 depicts the effect of the selective and potent D_2 dopamine receptor agonist PPHT on immunoreactive β-endorphin and immunoreactive dynorphin release from the perfused rat placenta fragments. It did not have any statistically significant effect on either immunoreactive β-endorphin or immunoreactive dynorphin. However, at a concentration of 10^{-5} M it did cause a minor but statistically non-significant increase of immunoreactive β-endorphin. PPHT did not have any effect on the release of immunoreactive dynorphin in the perfusion medium.

4. Discussion

The physiological role of placenta-derived opioids and the regulation of their production remain speculative. Placenta-derived β-endorphin, an endogenous μ-opioid agonist, may be primarily a myometrial quiescence-inducing agent and a regulator of stress response of the fetal-maternal unit. Placental-derived dynorphin may directly affect the placenta itself since the majority of opioid receptors in this tissue are of the κ type for which dynorphin is the principal endogenous ligand (Ahmed et al., 1989; Belisle et al., 1988). Indeed, it has been shown that dynorphin agonists stimulate the secretion of human Chorionic Gonadotropin (hCG) (Cemerikic et al., 1991; Barnea et al., 1991) and human Placenta Lactogen (hPL) (Belisle et al., 1988), and inhibit the secretion of acetylcholine from the villous trophoblast (Ahmed and Horst, 1986). Since acetylcholine regulates the uptake of amino acids from the maternal circulation by placental tissue, this may account for the low birth weight of newborns of pregnant heroin addicts (Ahmed et al., 1991). Furthermore, the intrauterine injection of an anti-dynorphin antiserum reduces the number of blastocyst implantations in rat suggesting yet another intrauterine role for this opioid (Zhang et al., 1991).

Our data showed that the general dopamine receptor agonists dopamine and apomorphine and the selective D_1 dopamine receptor agonist SKF-38393 stimulated the basal secretion of placental IR-β-endorphin, in an apparently dose-dependent manner, while the selective and potent D_2 dopamine receptor agonist PPHT had no effect. Thus, it appears that the stimulatory effect of dopamine on placental β-endorphin is mediated only by the D_1 dopamine receptor. This was confirmed by the use of the selective D_1 dopamine receptor antagonist SCH-23390, which blocked the dopamine- and SKF-38393-induced immunoreactive β-endorphin secretion. None of the dopaminergic agonists tested had any effect on the secretion of placental immunoreactive dynorphin.

The effect of dopamine receptor agonists on the basal secretion of opioids from rat placenta exhibited the following characteristics. (a) The effect of dopamine receptor

agonists was opioid type-specific since although the D_1 dopamine receptor agonists had a dose-dependent stimulatory effect on the secretion of immunoreactive β-endorphin, they did not have any effect on immunoreactive dynorphin. Differences in the regulation of placental opioids may mean that they have different effects. Indeed, β-endorphin and dynorphin may exert different physiological effects within the uterine cavity, a phenomenon well described in the central nervous system. Thus, it is possible that placenta-derived β-endorphin affects mainly the decidua and myometrium (which actually have mainly μ-opioid receptors) while the dynorphins may affect the placenta itself (which has mainly κ-opioid receptors). (b) The effect of dopamine appears to be mediated by the D_1 dopamine receptor. Both the D_1 and D_2 dopamine receptor types are present in placenta, while little is known about the other dopamine receptor types (i.e., D_3, D_4 and D_5). It is known that the D_1 dopamine receptor, which is generally stimulatory, induces the synthesis and accumulation of placental cAMP (Ferre, 1986), while the D_2 dopamine receptor, which is mainly inhibitory, decreases placental cAMP and inhibits Ca^{2+} influx in the placental trophoblast (Vaillancourt et al., 1994a). We found that only the D_1 dopamine receptor agonists were capable of affecting the basal secretion of immunoreactive β-endorphin, while the D_2 dopamine receptor agonists were ineffective. Thus, it appears that the regulation of the basal release of opioids in the rat placenta is different from that of the neurointermediate lobe of pituitary with regard to the type of the dopamine receptor involved, since the effect of dopamine on β-endorphin in the rat pituitary neurointermediate lobe is mediated by the D_2 dopamine receptor while in placenta it is mediated by the D_1 dopamine receptor. (c) The effect of dopamine on the secretion of rat placental β-endorphin is stimulatory: indeed, in contrast to the pituitary neurointermediate lobe, where dopamine suppresses the production and secretion of β-endorphin, in our experimental model dopamine stimulated the secretion of placental β-endorphin. It should be noted, however, that the former regulation is mediated by the dopamine D_2 receptor (Young et al., 1993), while the placental β-endorphin secretion appears to be mediated by the D_1 dopamine receptor, which is known to stimulate the formation of cAMP (Ogawa, 1995). (d) Placental dynorphin was not affected by the types of dopamine receptor agonists tested. However, it is known that dopamine affects the production of dynorphin at several central nervous system sites. Thus, dopamine originating from the nigrostriatal pathway stimulates both the secretion (Li et al., 1990; Gerfen et al., 1991) and synthesis of dynorphin in rat striatum (Steiner and Gerfen, 1995). However, it has also been shown that dopamine does not affect dynorphin in the anterior pituitary gonadotrophs (Schwaninger et al., 1987). Similarly, our data suggest that dopamine most probably has no effect on the secretion of placental dynorphin. It thus appears that in neural tissues dopamine plays a regulatory role vis-a-vis dynorphin while in non-neural tissues, for instance the gonadotrophs and placenta, this may not be the case.

In conclusion, our data suggest that dopamine affects the basal secretion of rat placental β-endorphin but not that of placental dynorphin. This effect of dopamine appears to be mediated via the D_1 dopamine receptor. These data can be of use in the interpretation of the effects of dopamine in the regulation of the fetal-maternal unit stress response, placental hormonal secretion and myometrial function.

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