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Effect of adenosine receptor agonists and antagonists on morphine-induced catalepsy in mice

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Abstract

Effects of adenosine receptor agonists and antagonists on morphine-induced catalepsy in mice were investigated. The adenosine agonists, NECA (5′-*N*-ethylcarboxamidoadenosine) and S-PIA (S(+)-N^6-(2-phenylisopropyl)adenosine) in doses which did not induce any response, increased the cataleptogenic effect produced by morphine. However, the morphine response was decreased and increased by the lower and higher doses of the adenosine receptor agonist, CHA (N^6-cyclohexyladenosine), respectively. The adenosine receptor antagonist, theophylline, decreased, but 8-phenyltheophylline increased, the response induced by morphine. Naloxone inhibited the catalepsy induced by morphine or morphine + NECA but not that induced by NECA alone. It is concluded that adenosine A_2 receptor activation increases, while adenosine A_1 receptor stimulation decreases, the morphine cataleptogenic response. The response to morphine may be mediated through opioid and adenosine receptor mechanisms. © 1997 Elsevier Science B.V.

Keywords: Morphine; Adenosine receptor agonist; Adenosine receptor antagonist; Naloxone; Catalepsy; (Mouse)

1. Introduction

Many drugs, including dopamine receptor antagonists (Carlsson and Lindquist, 1963; Van Rossum, 1966) and morphine (Beecham and Handley, 1974; Ariyanayagam and Handley, 1975; Muley et al., 1982), have been shown to induce catalepsy, an abnormal motor state in which animals maintain bizarre postures when so positioned by an experimenter (Munkvad et al., 1968). Administration of morphine peripherally (Vanderwende and Spoerlein, 1979) or injection of the drug into the nucleus accumbens (Winkler et al., 1982), the striatum (Costall et al., 1978; Havemann et al., 1980), the reticular formation (Dunstan et al., 1981) or the periaqueductal (Pert, 1977) of rodents induces catalepsy.

Administration of morphine has been reported to increase the release of purines in a variety of experimental preparations including the cortical cup (Phillis et al., 1979, 1980; Jiang et al., 1980) cortical slice (Fredholm and Vernet, 1978; Stone, 1981) and cortical prism (Wu et al., 1982).

Release of adenosine from the spinal cord in vivo, using an intrathecal perfusion system, has been demonstrated following injection of antinociceptive doses of morphine into the lateral ventricle (Sweeney et al., 1989). Release of adenosine from the spinal cord may mediate a significant component of the spinal antinociceptive action of morphine (Sawynok et al., 1989, 1991). The adenosine receptor antagonists, theophylline (Daly, 1982; Bruns et al., 1986) and 8-phenyltheophylline (Smellie et al., 1979b; Jacobson et al., 1985), have been shown to decrease morphine antinociception. In our previous study, we found that adenosine A_2 receptor stimulation could induce catalepsy (Zarrindast et al., 1993). In the present study, the effects of adenosine receptor agonists and antagonists on morphine-induced catalepsy were tested.

2. Materials and methods

2.1. Subjects

Male albino mice, weighing between 20–25 g were used in these experiments. The animals were housed in plastic cages in groups of up to 10 in a room maintained at

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22 ± 2°C on a 12 h light–dark cycle. Food and water were freely available except during the experiments. Each animal was used once.

2.2. Assessment of catalepsy

Catalepsy was measured by the 'bar test'. The forepaws of the mice were gently placed on a bar 0.3 cm in diameter and 20 cm long, which was fixed at a height of 5.5 cm above the working surface.

The length of time that the animals maintained this position was scored and recorded. Animals maintaining the cataleptic posture from 0 to 10 s were scored as 0; 10 to 150 s = 1; 151 to 300 s = 2; 301 to 600 s = 3; 601 to 1200 s = 4 and over 1200 s = 5.

Catalepsy scores were recorded at 15, 30, 45 and 60 min after drug injection.

2.3. Drugs

The following drugs were used: morphine HCl (MacFarlane Smith, UK); naloxone HCl (Dupont, Germany); NECA (5′-*N*-ethylcarboxamidoadenosine); S-PIA (S(+)-N^6-(2-phenylisopropyl)adenosine); CHA (N^6-cyclohexyladenosine); theophylline (1,3-dimethylxanthine) and 8-phenyltheophylline (Sigma, UK). The drugs were dissolved in normal saline except for 8-phenytheophylline which was dissolved in a drop of ethylenediamine then diluted with saline. All drugs were injected intraperitoneally (i.p.) except for morphine which was given subcutaneously (s.c.).

2.4. Statistical analysis

Analysis of variance (ANOVA) followed by the Newman–Keuls test was performed. $P < 0.05$ was considered significant.

3. Results

3.1. Catalepsy induced by morphine in mice

Subcutaneous (s.c.) injection of different doses of morphine (20, 30 and 40 mg/kg) to mice induced a dose-dependent cataleptogenic response ($F(12,104) = 74.69$, $P < 0.01$). The maximum effect was achieved 45 min after drug administration and with 40 mg/kg of the drug (Fig. 1).

3.2. The effect of adenosine receptor agonists on morphine-induced catalepsy

Intraperitoneal (i.p.) injection of different doses of NECA (0.025, 0.05 and 0.075 mg/kg) to mice, 15 min prior to morphine (20, 30 and 40 mg/kg, s.c.) caused an increase in the catalepsy induced by morphine ($F(11,96) = 62.1$, $P < 0.01$) (Fig. 2).

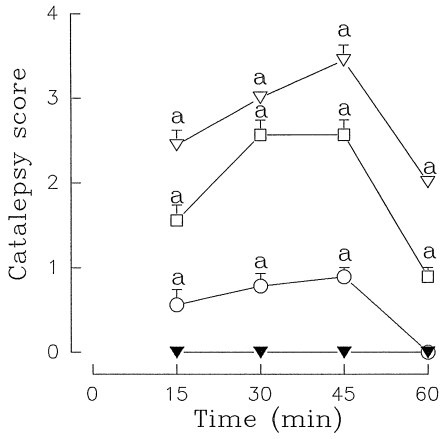

Fig. 1. Dose–response and time course of catalepsy after subcutaneous (s.c.) injection of morphine in mice. Groups of animals were given saline (▼), or morphine (○) 20, (□) 30 and (▽) 40 mg/kg. Each point is the mean ± S.E.M. of catalepsy in 9 mice. Catalepsy was recorded 15, 30, 45 and 60 min after drug administration. [a]$P < 0.01$ different from saline control group.

Administration of different doses of S-PIA (0.075, 0.15 and 0.3 mg/kg, i.p.) to mice, 15 min prior to morphine (20, 30 and 40 mg/kg, s.c.) increased the catalepsy produced by morphine ($F(11,96) = 74.63$, $P < 0.01$) (Fig. 3).

Treatment of the animals with low doses of CHA (0.02, 0.04 and 0.06 mg/kg, i.p.) 15 min before morphine administration, decreased, while high doses of CHA (0.3 and 0.4 mg/kg, 15 min, i.p.) increased the morphine response ($F(17,144) = 76.47$, $P < 0.01$) (Fig. 4).

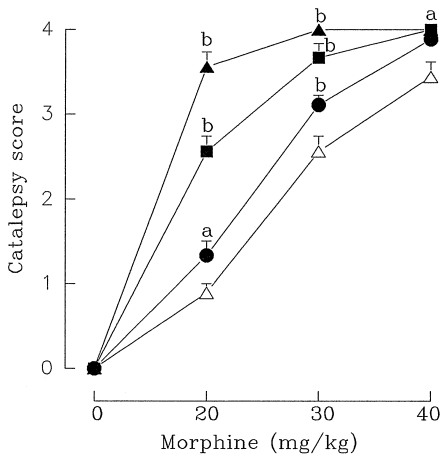

Fig. 2. Effects of NECA on morphine-induced catalepsy. Animals were injected with different doses of morphine (△; 20, 30 and 40 mg/kg; s.c.) alone, or with NECA (●) 0.025, (■) 0.05 and (▲) 0.075 mg/kg; i.p., 15 min prior to morphine administration. Each point is the mean ± S.E.M. of catalepsy in 9 mice. Catalepsy was recorded 45 min after morphine injection. [a]$P < 0.05$, [b]$P < 0.01$ different from morphine control groups.

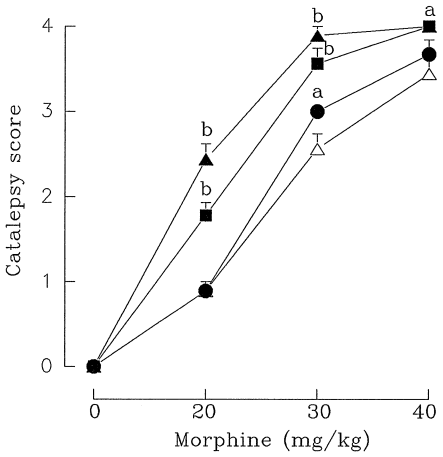

Fig. 3. Effects of S-PIA on morphine-induced catalepsy. Animals were injected with different doses of morphine (△; 20, 30 and 40 mg/kg; s.c.) alone, or with S-PIA (●) 0.075, (■) 0.15 and (▲) 0.3 mg/kg; i.p., 15 min prior to morphine administration. Each points is the mean ± S.E.M. of catalepsy in 9 experiments. Catalepsy was recorded 45 min after morphine injection. [a]$P < 0.05$, [b]$P < 0.01$ different from morphine control groups.

3.3. The effect of adenosine receptor antagonists on morphine-induced catalepsy

When the animals were treated with different doses of theophylline (0.5, 1 and 2.5 mg/kg, i.p.) 30 min prior to morphine, the catalepsy induced by morphine was decreased ($F(11,96) = 104.98$, $P < 0.01$). However, when the animals were treated with different doses of 8-phenyltheophylline (0.5, 1 and 2 mg/kg, i.p.) 30 min before morphine, the catalepsy was increased by the drug ($F(11,96) = 71.14$, $P < 0.01$) (Fig. 5).

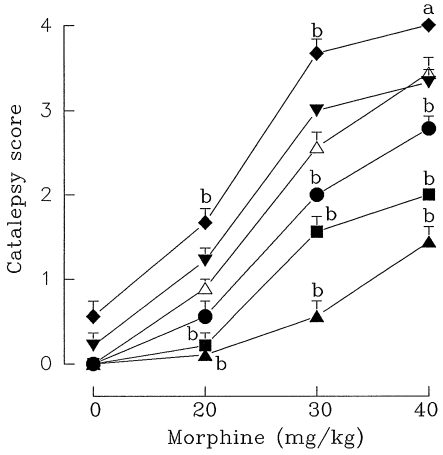

Fig. 4. Effects of CHA on morphine-induced catalepsy. Animals were injected with different doses of morphine (△; 20, 30 and 40 mg/kg; s.c.) alone, or with CHA (●) 0.02, (■) 0.04, (▲) 0.06, (▼) 0.3 and (◆) 0.4 mg/kg; I0, 15 min prior to morphine administration. Each point is the mean ± S.E.M. of catalepsy in 9 mice. Catalepsy was recorded 45 min after morphine injection. [a]$P < 0.05$, [b]$P < 0.01$ different from morphine control groups.

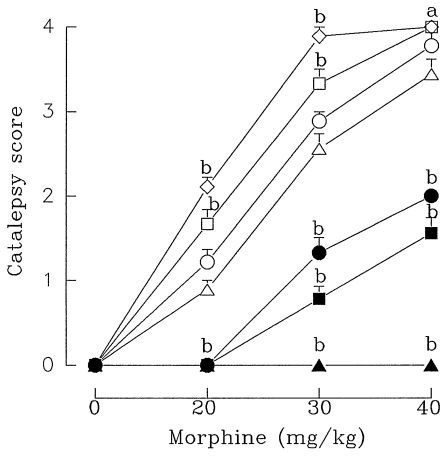

Fig. 5. Effects of adenosine receptor antagonists on morphine-induced catalepsy. Animals were injected with different doses of morphine (△; 20, 30 and 40 mg/kg; s.c.) alone, or theophylline (●) 0.5, (■) 1 and (▲) 2.5 mg/kg; i.p., or 8-phenyltheophylline (○) 0.5, (□) 1 and (◇) 2 mg/kg; i.p., 30 min prior to morphine administration. Each point is the mean ± S.E.M. of catalepsy in 9 mice. Catalepsy was recorded 45 min after morphine injection. [a]$P < 0.05$, [b]$P < 0.01$ different from morphine control groups.

3.4. The effects of naloxone on catalepsy induced by morphine or / and NECA

Pretreatment of animals with naloxone (5 and 10 mg/kg, 1 min, i.p.) inhibited the cataleptogenic response to different doses of morphine or morphine plus NECA, but not that to NECA alone ($F(16,136) = 133.53$, $P < 0.01$) (Table 1).

Table 1
Effects of naloxone on catalepsy induced by morphine or/and NECA in mice

Treatment (mg/kg)	Catalepsy score (mean ± S.E.M.)
Saline	0.00 ± 0.00
Morphine 20	0.89 ± 0.11
Morphine 20 + Naloxone 5	0.00 ± 0.00[a]
Morphine 20 + Naloxone 10	0.00 ± 0.00[a]
Morphine 40	3.44 ± 0.18
Morphine 40 + Naloxone 5	0.33 ± 0.17[a]
Morphine 40 + Naloxone 10	0.00 ± 0.0[a]
NECA 0.5	1.44 ± 0.18
NECA 0.5 + Naloxone 5	1.22 ± 0.15
NECA 0.5 + Naloxone 10	1.56 ± 0.18
NECA 0.05	0.00 ± 0.00
NECA 0.05 + Morphine 20	2.56 ± 0.18
NECA 0.05 + Morphine 20 + Naloxone 5	0.00 ± 0.00[a]
NECA 0.05 + Morphine 20 + Naloxone 10	0.00 ± 0.00[a]
NECA 0.05 + Morphine 40	4.00 ± 0.00
NECA 0.05 + Morphine 40 + Naloxone 5	0.33 ± 0.17[a]
NECA 0.05 + Morphine 40 + Naloxone 10	0.00 ± 0.00[a]

Naloxone was injected immediately and NECA 15 min before morphine injection. Data represent the mean ± S.E.M. of catalepsy of 9 mice. Catalepsy was recorded 45 min after the morphine injection.
[a]$P < 0.01$ difference is statistically significant.

4. Discussion

The inhibition of striatal dopamine receptor sites induces catalepsy in rodents (Carlsson and Lindquist, 1963; Van Rossum, 1966). However, it has been shown that, morphine, unlike dopamine receptor antagonists, does not induce catalepsy through the inhibition of postsynaptic striatal dopamine receptors (Muley et al., 1982). The opioid also does not change the basal activity of the dopamine-sensitive adenylyl cyclase and also does not antagonize the stimulation of the enzyme in striatal homogenates of mouse brain (Racagni et al., 1979).

The antinociceptive effect of morphine has been attributed partly to the release of adenosine in both spinal and supraspinal sites (Sweeney et al., 1989; Sawynok et al., 1991). We previously provided evidence for the involvement of adenosine mechanisms in catalepsy (Zarrindast et al., 1993) and effects of adenosine receptor activation on morphine antinociception (Zarrindast and Nikfar, 1993). The possibility may exist that morphine induces the catalepsy through the adenosinergic system(s).

Adenosine functions through at least two sites which have been termed adenosine A_1 and A_2 receptors. Adenosine A_1 or A_2 receptors mediate decreases or increases in the levels of cAMP, respectively (Van Calker et al., 1979; Londos et al., 1980; Freissmuth et al., 1991). Our present results indicate that adenosine receptor agonists, NECA (Daly et al., 1986a) and S-PIA (Smellie et al., 1979a; Daly et al., 1986b) increase the morphine response dose dependently. The order of potency at the adenosine A_1 receptors is PIA > NECA and at the adenosine A_2 receptors NECA > S-PIA (Bruns et al., 1986; Sawynok and Sweeney, 1989). Adenosine A_2 receptor stimulation has been shown to induce catalepsy (Zarrindast et al., 1993; Kanda et al., 1994) and causes antinociception (Delander and Hopkins, 1987). One can expect that the catalepsy response to morphine is associated with an adenosine A_2 receptor mechanism(s). The present data show that the adenosine receptor agonist, CHA (Moos et al., 1985), with greater affinity for adenosine A_1 receptors (Bruns et al., 1986) at high doses increased, while at low doses it decreased the morphine-induced catalepsy. The possibility that adenosine A_1 receptor activation by low doses of CHA decreases the morphine-induced catalepsy seems likely. There is a possibility that adenosine A_2 receptor activation mediates the response elicited by high doses of the adenosine receptor agonist, CHA. This is further suggested by the fact that the adenosine A_1 receptor antagonist, 8-phenyltheophylline (Smellie et al., 1979b; Jacobson et al., 1985; Bruns et al., 1986), increased the morphine response. This observation appears consistent with those reported previously (Zarrindast et al., 1993) that adenosine A_2 receptor activation induces, while adenosine A_1 receptor stimulation decreases catalepsy. However, there are data indicating that 8-phenyltheophylline penetrates the brain poorly (Fredholm et al., 1983). Since our previous experiments showed that 8-phenyltheophylline influences centrally mediated behaviour (Zarrindast and Nikfar, 1993; Zarrindast et al., 1993, 1995), this could not be the case. Other possibilities should also be considered. The adenosine A_2 receptors are subdivided into two subtypes, A_{2A} and A_{2B} (Daly et al., 1983; Bruns et al., 1986) and the adenosine A_{2A} receptor mechanism has been implicated in the catalepsy (Kanda et al., 1994). The existence of other subtypes of adenosine receptors named A_3 (Zhou et al., 1992) and A_4 (Cornfield et al., 1992) has been proposed; therefore the possibility should be considered of involvement of an as yet unknown subtype of adenosine receptor, with different effects of adenosine A_{2A} and A_{2B} receptors and non-specific effects shared by these agents or even pharmacokinetic interactions by the drugs.

In the present work, the adenosine receptor antagonist, theophylline (Daly, 1982; Daly et al., 1983; Bruns et al., 1986), decreased the catalepsy induced by morphine in a dose-dependent manner. It has been suggested that theophylline reduces the catalepsy induced by dopamine receptor antagonists (Duk et al., 1991). Moreover, methylxanthines have been shown to act as dopamine receptor agonists (Watanabe et al., 1981; Ungerstedt et al., 1981; Herrera-Marschitz et al., 1988; Casas et al., 1989; Ferre et al., 1991). There is a possibility that theophylline induces the present response through a dopaminergic mechanism.

Theophylline has been shown to reduce the catalepsy induced by adenosine agonists (Zarrindast et al., 1993), and also to decrease the morphine antinociception (Ho et al., 1973; Zarrindast and Nikfar, 1993). The drug has been shown to have both A_1 and A_2 antagonistic properties (Daly et al., 1981; Schawbe et al., 1985), however there is a report indicating the prevalence of an adenosine A_2 receptor antagonistic effect for the drug (Ferre et al., 1991). Blockade of the adenosine A_{2A} receptor subtype has been suggested to antagonize catalepsy (Kanda et al., 1994). To find whether theophylline induces its response by such a mechanism(s) requires further experiments.

Our data showed that the catalepsy induced by morphine was antagonized by the opioid receptor antagonist, naloxone. The results may support other findings (Beecham and Handley, 1974; Ariyanayagam and Handley, 1975; Muley et al., 1982) that opioid receptor antagonists effectively antagonized morphine catalepsy in the mouse.

We have found that naloxone failed to alter NECA-induced catalepsy, suggesting that opioid mechanisms are not involved in mediating adenosine-induced catalepsy. However, the catalepsy induced by morphine plus NECA was antagonized by naloxone, suggesting that the interaction of morphine with the adenosine system may be mediated through specific opioid receptors.

Overall, it should be considered that adenosine receptor agonists agents may produce cardiovascular effects, sedation, myorelaxation or hypothermia which may influence the catalepsy response. However, the adenosine receptor agonists which act differently on catalepsy in the present

study, all reduced mouse body temperature (Bowker and Chapman, 1986; Zarrindast and Heidari, 1993).

To evaluate the exact effects of adenosine agents on morphine-induced catalepsy may require more experiments.

References

Ariyanayagam, A.D., Handley, S.L., 1975. Effect of sensory stimulation on the potency of cataleptogens. Psychopharmacologia (Berlin) 41, 165–167.

Beecham, I.J., Handley, S.L., 1974. Potentiation of catalepsy induced by narcotic agents during Haffners test for analgesia. Psychopharmacologia 40, 157–164.

Bowker, H.M., Chapman, A.G., 1986. Adenosine analogues. The temperature-dependence of the anticonvulsant effect and inhibition of 3H-D-aspartate release. Biochem. Pharmacol. 35, 2949–2953.

Bruns, R.F., Lu, G.H., Pugsley, T.A., 1986. Characterization of the A_2 adenosine receptor labelled by [^{3}H]NECA in rat striatal membrane. Mol. Pharmacol. 29, 331–346.

Carlsson, A., Lindquist, M., 1963. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. Toxicol. 20, 140–144.

Casas, M., Feree, S., Cobos, A., Grau, J.M., Jane, F., 1989. Relationship between rotational behaviour induced by apomorphine and caffeine in rats with unilateral lesion of the nugrostriatal pathways. Neuropharmacology 28, 407–409.

Cornfield, L.J., Hu, S., Hurt, S.D., Sills, M.A., 1992. [3H]2-Phenylaminoadenosine ([3H] CV 1808] labels a novel adenosine receptor in rat brain. J. Pharmacol. Exp. Ther. 263, 552–561.

Costall, B., Fortune, D.H., Naylor, R.J., 1978. Involvement of mesolimbic and extrapyramidal nuclei in the motor depressant action of narcotic drugs. J. Pharm. Pharmacol. 30, 566–572.

Daly, J.W., 1982. Adenosine receptors: Targets for future drugs. J. Med. Chem. 25, 197–207.

Daly, J.W., Bruns, R.F., Snyder, S.H., 1981. Adenosine receptors in the central nervous system: Relationship to the central actions of methylxanthines. Life Sci. 28, 2083–2097.

Daly, J.W., Butts-Lamb, P., Padgett, W., 1983. Subclasses of adenosine receptors in the central nervous system: Interaction with caffeine and related methylxanthines. Cell Mol. Neurobiol. 3, 69–80.

Daly, J.W., Padgeh, W.L., Shamin, M.T., 1986a. Analogs of caffeine and theophylline effect of structural on affinity at adenosine receptors. J. Med. Chem. 29, 1305–1308.

Daly, J.W., Padgeh, W., Thompson, R.D., Kushachi, S., Bugni, W.J., Olsson, R.A., 1986b. Structure–activity relationship for N^6-substituted adenosine at a brain A_1 adenosine receptor with comparison to an A_2 adenosine receptor regulating coronary blood flow. Biochem. Pharmacol. 35, 2467–2481.

Delander, G., Hopkins, C.J., 1987. Interdependence of spinal adenosinergic, serotonergic and noradrenergic systems mediating antinociception. Neuropharmacology 26, 1791–1794.

Duk, S., Krugers, J., Korf, J., 1991. The effect of theophylline and immobilization stress on haloperidol-induced catalepsy and on metabolism in the striatum and hippocampus, studied with lactography. Neuropharmacology 30, 469–473.

Dunstan, R., Broekkamp, C.L., Lloyd, K.G., 1981. Involvement of caudate nucleus, amygdala or reticular formation in neuroleptic and narcotic catalepsy. Pharmacol. Biochem. Behav. 14, 169–174.

Ferre, S., Herrera-Marschits, M., Grabowska-Anden, M., Casas, M., Ungerstedt, U., Anden, N.E., 1991. Postsynaptic dopamine/adenosine interaction: II. Postsynaptic dopamine agonism and adenosine antagonism of methylxanthines in short-term reserpinized mice. Eur. J. Pharmacol. 192, 31–37.

Fredholm, B.B., Vernet, L., 1978. Morphine increase depolarization induced purine release from rat cortical slices. Acta Physiol. Scand. 104, 502–504.

Fredholm, B.B., Herrera-Marschitz, M., Jonzon, B., Lindstrom, K., Ungerstedt, U., 1983. On the mechanism by which methylxanthines enhance apomorphine-induced rotation behaviour in the rat. Pharmacol. Biochem. Behav. 19, 535–541.

Freissmuth, M., Selzer, E., Schuts, W., 1991. Interaction of purified bovine brain A_1 adenosine receptors with G-proteins. Biochem. J. 275, 651–656.

Havemann, U., Winkler, M., Kuschinsky, K., 1980. Opioid receptors in the caudate nucleus can mediate EMG recorded rigidity in rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 313, 139–144.

Herrera-Marschitz, M., Casas, M., Ungerstedt, U., 1988. Caffeine produces contralateral rotation in rats with unilateral dopamine enervation: Comparisons with apomorphine-induced responses. Psychopharmacology 94, 38–45.

Ho, I.K., Loh, H.H., Way, E.L., 1973. Cyclic adenosine monophosphate antagonism of morphine analgesia. J. Pharmacol. Exp. Ther. 185, 336–346.

Jacobson, K.A., Kirk, K.L., Daly, J.W., Jonzon, B., Li, Y.O., Fredholm, B.B., 1985. A novel 8-phenyl-substituted xanthine derivative is a selective antagonist at adenosine A_1 receptor in vivo. Arch. Physiol. Scand. 125, 341–342.

Jiang, Z.G., Chelack, B.J., Phillis, J.W., 1980. Effects of morphine and caffeine on adenosine release from rat cerebral cortex: Is caffeine a morphine antagonist. Can. J. Physiol. Pharmacol. 58, 1513–1515.

Kanda, T., Shiozaki, S., Shimada, J., Suzoki, F., Nakamura, J., 1994. KF17837: A novel selective adenosine A_{2A} receptor antagonist with anticataleptic activity. Eur. J. Pharmacol. 256, 263–268.

Londos, C., Cooper, D.M.F., Wolf, J., 1980. Subclasses of external adenosine receptors. Proc. Natl. Acad. Sci. USA 77, 2551–2554.

Moos, W.H., Szotek, D.S., Bruns, R.F., 1985. N^6-cycloalkyladenosines: Potent, A_1 selective adenosine agonists. J. Med. Chem. 28, 1383–1384.

Muley, M.P., Balsara, J.J., Jadhav, J.H., Chandorkar, A.G., 1982. Involvement of histaminergic mechanisms in the cataleptogenic effect of morphine in mice. J. Pharm. Pharmacol. 34, 34–37.

Munkvad, I., Pakkenberg, H., Pandrup, A., 1968. Aminergic systems in the basal ganglia associated with stereotyped hyperactive behaviour and catalepsy. Brain Behav. Evol. 1, 89–100.

Pert, A., 1977. Central sites involved in opiate actions. In: Fishman, J. (Ed.), The Based of Addiction. Berlin Dahlem Konferenzen, pp. 299–332.

Phillis, J.W., Jiang, Z.G., Chelack, B.J., Wu, P.H., 1979. Morphine enhances adenosine release from the in vivo rat cerebral cortex. Eur. J. Pharmacol. 65, 97–100.

Phillis, J.W., Jiang, Z.G., Chelack, B.J., Wu, P.H., 1980. The effect of morphine on purine and acetylcholine release from rat cerebral cortex: Evidence for a purinergic component in morphines action. Pharmacol. Biochem. Behav. 13, 421–427.

Racagni, G., Bruno, F., Iuliano, E., Paoletti, R., 1979. Differential sensitivity to morphine-induced analgesia and motor activity in two inbred strains of mice: Behavioral and biochemical correlations. J. Pharmacol. Exp. Ther. 209, 111–116.

Sawynok, J., Sweeney, M.I., 1989. The role of purines in nociception. Neuroscience 32, 557–569.

Sawynok, J., Sweeney, M.I., White, T.D., 1989. Adenosine release may mediate spinal analgesia by morphine. Trends Pharmacol. Sci. 10, 186–189.

Sawynok, J., Espey, M.J., Reid, A., 1991. 8-Phenyltheophylline reverses the antinociceptive action of morphine in the periaqueductal gray. Neuropharmacology 30, 871–877.

Schawbe, U., Ukena, D., Lohse, M.J., 1985. Xanthines derivatives as antagonists at A1 and A2 adenosine receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 330, 212–221.

Smellie, F.W., Daly, J.W., Dunwiddie, T.V., Hoffer, B.J., 1979a. The dextro and levorotatory isomers of phenylisoproryl-adenosine: Stereospecific effects on cyclic AMP formation and evoked synaptic responses in brain slices. Life Sci. 25, 1739–1748.

Smellie, F.W., Davis, C.W., Daly, J.W., Wells, J.N., 1979b. Alkylxanthines inhibition of adenosine-elicited accumulation of cyclic AMP in brain slices and brain phosphodiesterase activity. Life Sci. 24, 2475–2482.

Stone, T.W., 1981. The effects of morphine and methionine-enkephalin on the release of purines from cerebral cortex slices of rats and mice. Br. J. Pharmacol. 74, 171–176.

Sweeney, M.I., White, T.D., Sawynok, J., 1989. Adenosine release from the spinal cord may mediate antinociception by intracerebroventricular morphine. Soc. Neurosci. Abstr. 15, 371.

Ungerstedt, U., Herrera-Marschitz, M., Casa, M., 1981. Are apomorphine, bromocriptine and methylxanthines agonist at the same dopamine receptor? In: Gessa, G.L., Corsini, G.W. (Eds.), Apomorphine and Other Dopaminergics, vol. I, Basic Pharmacology. Raven Press, New York, NY, 85 pp.

Van Calker, D., Muller, M., Hamprechi, B., 1979. Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. J. Neurochem. 33, 999–1005.

Van Rossum, J.M., 1966. The significance of dopamine receptor blockade for the mechanism of action of neuroleptic drugs. Arch. Int. Pharmacodyn. 160, 492–494.

Vanderwende, C., Spoerlein, M.T., 1979. Morphine-induced catalepsy in mice. Modification by drugs acting on neurotransmitter system. Neuropharmacology 18, 633–637.

Watanabe, H., Ikeda, M., Watanabe, K.J., 1981. Properties of rotational behaviour produced by methylxanthine-induced lesions. Pharm. Dyn. 4, 301–307.

Winkler, M., Havmann, U., Kushinsky, K., 1982. Unilateral injection of morphine into the nucleus accumbens induces akinesia and catalepsy, but no spontaneous muscular rigidity in rats. Naunyn Schmiedeberg's Arch. Pharmacol. 318, 143–147.

Wu, P.H., Phillis, J.W., Yuen, H., 1982. Morphine enhances the release of ^{3}H-purines from rat brian cerebral cortical prisms. Pharmacol. Biochem. Behav. 17, 749–755.

Zarrindast, M.R., Heidari, M.R., 1993. Involvement of adenosine receptors in mouse thermoregulation. J. Psychopharmacol. 7, 365–370.

Zarrindast, M.R., Fatehi, F., Mohagheghi-Badi, M., 1995. Effects of adenosine agents on apomorphine-induced yawning in rats. Psychopharmacology 122, 292–296.

Zarrindast, M.R., Modabber, M., Sabetkasai, M., 1993. Influences of different adenosine receptor subtypes on catalepsy in mice. Psychopharmacology 107, 163–167.

Zarrindast, M.R., Nikfar, Sh., 1993. Different influences of adenosine receptor agonists and antagonists on morphine antinociception in mice. Gen. Pharmacol. 25, 139–142.

Zhou, Q.Y., Li, C., Olah, M.E., Johnson, R.A., Stiles, G.L., Giveli, O., 1992. Molecular cloning and characterization of an adenosine receptor: The A3 receptor. Proc. Natl. Acad. Sci. USA 89, 7432–7436.