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CEREBRAL BLOOD FLOW REGULATION IN ANESTHETIZED MORPHINE DEPENDENT RATS: THE ROLE OF THE ADENOSINE SYSTEM

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ABSTRACT

Adenosine has many of the characteristics of a regulator of cerebral blood flow and adenosine receptors change in morphine dependency. In this study the changes in adenosine receptors' responsiveness of pial vessels in the hindlimb area of the sensory cortex were evaluated in morphine dependent rats (MDR) using the laser Doppler flowmetry technique. Adult male Sprague Dawley rats (250-350 g) were used in all experiments. Animals were made morphine dependent, thereafter local effects of adenosine receptor agonists and antagonists on regional cerebral blood flow (rCBF) were investigated.

Results obtained in this study show that adenosine (10^{-5}, 10^{-4}, 10^{-3}M) increases rCBF in a dose dependent manner in sham operated, control and MDR, so that the increase of rCBF in MDR is statistically significant ($p<0.01$). This response was inhibited by theophylline (5×10^{-5}M). Lidocaine (2%) reduced adenosine-induced increase in rCBF of MDR. N6-cyclohexyladenosine (10^{-6}, 10^{-5}, 10^{-4} M) and 8-cyclopentyltheophylline (10^{-6}M) as a selective agonist and antagonist of adenosine A1 receptors had no significant effect on rCBF in control and MDR. CGS-21680 (10–6 M) as a selective adenosine A2a receptor agonist, increased rCBF in MDR significantly ($p<0.05$). This response was antagonized by ZM-241385. NECA (10–^{6}M) as a adenosine A2b receptor agonist, increased rCBF in MDR significantly ($p<0.05$). This response was antagonized by Alloxazine. The results of this study indicate an increase in adenosine A2 receptors' (including A2a and A2b subtypes) responsiveness in hind limb sensory cortex of MDR.

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Keywords: Cerebral blood flow; Morphine dependent rat.

INTRODUCTION

Opiate agonist drugs have multiple actions both centrally as well as peripherally. Their most prominent central effects include potent analgesia, sedation, etc.[1] They also posses both direct reinforcing properties as well as the ability to enhance the affective quality of other reinforcing agents (e.g., brain stimulation reward). It is likely that this multiplicity of actions requires activation at multiple independent brain sites or circuits and is mediated by several opioid receptor types.[2] In addition, numerous nonopioid neurotransmitter systems including, but not limited to, a putative dopaminergic involvement in reinforcing are engaged by these agents.[3] Opioids are involved in the regulation of cerebral hemodynamics.

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Opioid receptor binding has been demonstrated on cerebral microvessels.[4] Enkephalin and dynorphin immunoreactivity have been shown in large cerebral arteries of the pig. Opioids such as methionine-enkephalin and leucine enkephalin induce cerebral vasodilation while dynorphin produces tone dependent effects, dilation during normotension and vasoconstriction during hypotension.[5] In these effects, nitric oxide (NO) and cGMP contributes to opioid-mediated pial artery vasodilation.[6]

Adenosine is an endogenous neuromodulator that generally has inhibitory effects on brain function. In addition it has been implicated in mediating both acute and chronic opiate effects.[7] It also has regulatory effects on cerebral blood flow.[8] Many studies have demonstrated opioid-adenosine interaction at a cellular level.[9] Adenosine has often been implicated as a mediator of the effects of morphine, since methylxanthines which are adenosine receptor antagonists, have been shown to block antinociception produced by intrathecal morphine administration and to reduce morphine induced hypotension.[10] Adenosine and morphine induce a dose-dependent decrease in diastolic blood pressure in the anesthetized rat. These effects were attenuated by adenosine A1 receptor antagonist.[11] Our previous studies and other researches indicate changes in number and function of adenosine receptors in different regions of the brain of morphine dependent animals. For example, down regulation of adenosine A1 and up regulation of adenosine A2 receptors in the nucleus tractus solitarius of the morphine dependent rat,[12] increase in adenosine A1 receptor in the cortex of morphine dependent mice, and up-regulation of adenosine transporter binding site in striatum and hypothalamus of opiate tolerant mice.[13] Other investigators also have reported increase in the sensitivity of nucleus paragigantocellularis neuron to adenosine receptor ligands in MDR.[14] On the other hand we indicated that morphine and naloxone have profound effects on cerebral blood flow (CBF) in MDR.[15] Therefore regarding the effects of the adenosine system on CBF and the changes of adenosine receptors in the MDR, the aim of this study was to investigate the adaptive changes of adenosine receptors in the sensory cortex of MDR and the effects of these changes on CBF.

MATERIAL AND METHODS

Induction of morphine dependency

Adult male Sprague-Dawley rats (250-350 g) were used in all experiments. The animals were housed in groups of 3-5 and maintained on pellets and water ad libitum. One group, as the sham-operated group, received tap water; the second group, as the control group, received 3% sucrose in tap water and the third group, as the dependent group, received morphine sulfate and 3% sucrose in tap water. Rats were made morphine dependent by chronic administration of morphine sulfate 0.1, 0.2, 0.3 mg/mL each for 48 h and 0.4 mg/mL/day for up to 21 days, in their drinking water. The withdrawal syndrome signs precipitated by naloxone (3 mg/kg, s.c.) were used and recorded for an hour, as indicators of the development of morphine dependency.

Animal preparation

Animals were anesthetized with urethane (1.5 g/kg, i.p.) and placed on a heating pad (Narco Bio-system) to maintain a constant rectal temperature (37± 0.5°C). After a tracheotomy, the rats were allowed to breathe spontaneously. The arterial oxygen saturation percent was monitored continuously with pulse oximeter (Radiometer-Copenhagen). Catheters were placed in the femoral artery for measurement of systemic arterial blood pressure and heart rate (P-1000B pressure transducer, Narco Bio-system) and in the carotid artery for withdrawing and sampling of the arterial blood. The blood was collected periodically for blood gas and pH determination (AVL 993).

Measurement of cerebral blood flow

Laser-Doppler flow meter (MBF3D, Moor instrument, Axminster, UK) was used in this study for recording CBF. The animals were mounted in a stereotaxic frame and a 2 mm diameter hole was drilled in the skull above the parietal cortex, 2 mm caudal to bregma, and 2.7 mm lateral to midline. This point lies over the hind limb area of the sensory cortex (Paxinos and Watson, 1986). The dura matter was resected with caution and prewarmed (37°C) artificial cerebrospinal fluid (aCSF) suffused over the cortical surface.The composition (in mmol/L) of the aCSF was as follows: 131.9 NaCl, 2.95 KCl, 1.25 $CaCl_2$, 0.665 $MgCl_2$, 24.6 $NaHCO_3$, 6.7 Urea and 3.7 D glucose (pH 7.4) . The 1mm diameter needle probe of the Laser Doppler flow meter was placed over the pial artery in the hole and advanced into the CSF ~0.2 mm above the surface of the cortex. Recordings were allowed to stabilize for at least 30 min before obtaining baseline flow levels.

In order to determine the responses of resting pial arteries to adenosine (10^{-5}, 10^{-4},10^{-3} M), cyclohexyladenosine (CHA, 10^{-6}, 10^{-5},10^{-4} M), CGS-21680 (10^{-6} M) and NECA (10^{-6} M), the cortical surface was suffused with aCSF containing adenosine and each agonist, respectively. The inhibitory effects of the theophylline (5×10 –5M), cyclopentyltheophylline (CPT), ZM-241385 and alloxazine (10^{-6}M) were determined alone and on the responses elicited by agonists. The antagonists were applied 30 min before and during suffusion of agonists.

At the end of the experiment the animals were sacrificed with a saturated solution of KCl injected intrave-

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nously and the biological zero values were measured. The biological zero values were subtracted from the flow values before calculation of percentage changes in blood flow. The time line of the experiments are indicated in Figure 1.

Drugs

Adenosine, theophylline, N6-cyclohexyladenosine (CHA), naloxone hydrocholoride, 5`-N-ethylcarboxamido-adenosine (NECA) and alloxazine (benzo[g] pteridine-2,4 (1H,3H) -dione) were purchased from Sigma Chemical Co., Morphine sulfate from Temad Co-Iran, lidocaine from Pasteur institute-Iran, sucrose and urethane from Merck, 8-cyclopentyltheophylline (CPT) from Research Biochemicals International, ZM-241385 (4-2-[7-amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a] [1,3,5]triazin-5-ylamino]ethyl)phenol) and CGS-21680,2-[p-(2-carboxyethyl)-phenethylamino]-5`-N-ethylcarboxamido adenosine were obtained from Tocris Cookson Ltd. Alloxazine and ZM-241385 were dissolved in dimethyl sulfoxide (DMSO) to make a stock solution of 10 mM/L. The final concentration of DMSO used in this study was 0.01%. Other drugs were dissolved in water, saline and aCSF.

Statistical analysis

Student's paired t-test was used to determine the significance of the differences in CBF changes between various treatment groups. The data were subjected to one and two-way analysis of variance (ANOVA) followed by a protected Tukey's test for multiple comparisons, as needed. Values are means ±SEM and a $p<0.05$ was accepted as statistically significant.

RESULTS

Test of dependence to morphine

Fig.2 shows the results of the withdrawal syndrome test, precipitated by injection of naloxone (3 mg/kg s.c) in the scruff of the neck, which was recorded for an hour.

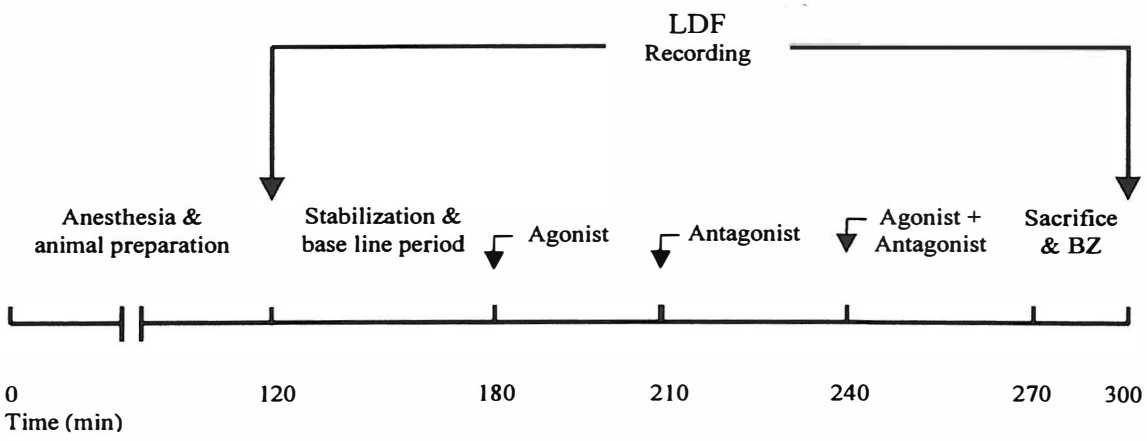

Fig. 1. Experimental protocol; timeline and order of experimental treatments and measures (B.Z: biological zero, LDF: laser Doppler flowmetry).

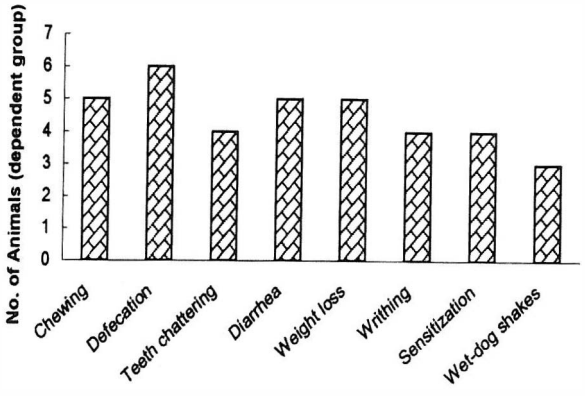

Fig. 2. Withdrawal signs precipitated by naloxone (3 mg/kg; s.c.) in morphine-dependent rats (n=6).

Defecation, diarrhea, chewing, weight loss, teeth chattering, writhing, sensitization and wet-dog shake were common among all morphine treated rats (n=6). Control rats (n=5) did not show any defined withdrawal signs.

Effects of adenosine and theophylline on rCBF

Adenosine (10^{-5}M) increased regional cerebral blood flow (rCBF) in the hind limb area of the sensory cortex in sham operated, control and morphine dependent rats (MDR) 10.02, 11.4 and 13.04 percent respectively. Although the response was higher in MDR, it was not statistically significant. Adenosine (10^{-4}M) increased rCBF in sham operated, control and MDR, 16.53, 17.01 and 25.17 percent respectively so that the increase of rCBF

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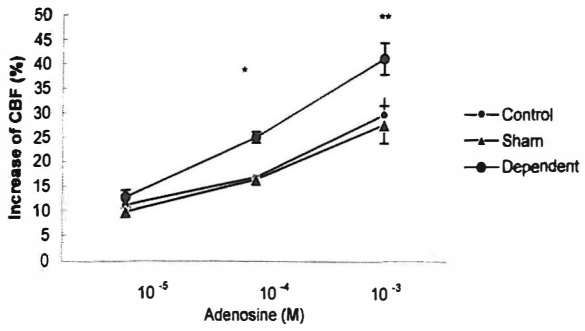

Fig. 3. Local effects of adenosine (10–5, 10 –4, 10 –3 M) on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n =7). *p< 0.05 and **p< 0.01, relative to control and sham operated animals.

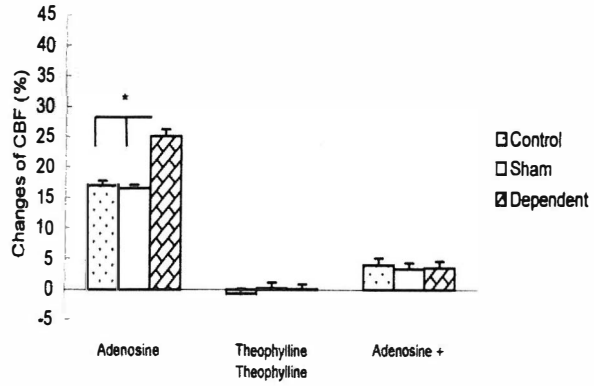

Fig. 4. Local effects of adenosine (10^{-4}M), theophylline (5×10^{-5} M), and adenosine (10^{-4}M) + theophylline (5×10^{-5} M) on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n =7). *p< 0.05, relative to control and sham operated animals.

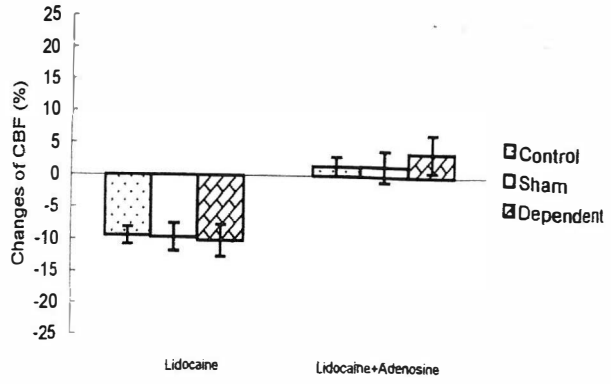

Fig. 5. Local effects of lidocaine 2% and lidocaine + adenosine (10^{-4} M) on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n= 5).

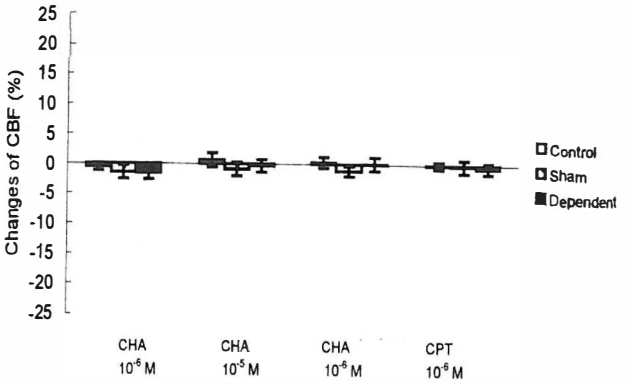

Fig. 6. Local effects of cyclohexyladenosine (CHA, 10^{-6}, 10^{-5}, 10^{-4} M) and cyclopentyltheophylline (CPT, 10^{-6} M) on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n= 9).

in MDR was statistically significant (p<0.05). Also adenosine (10^{-3}M) increased CBF so that increase of CBF in MDR was statistically significant (p<0.01). The dose response curve of adenosine is indicated in Fig 3. The effect of adenosine (10^{-4} M) on rCBF was inhibited by theophylline (5×10^{-5}M), although it alone has no significant effects on rCBF (Fig. 4).

Effects of lidocaine and adenosine on rCBF

Application of 100 µL lidocaine (2%) on the sensory cortex decreased rCBF in sham operated, control and MDR, 9.7, 9.5 and 10.16 percent respectively. Application of adenosine (10^{-4} M) together with lidocaine in sham operated, control and MDR increased rCBF 11.2, 10.96 and 13.8 percent respectively compared to base line of lidocaine. The difference between groups were not statistically significant (Fig .5).

Effects of CHA and CPT on rCBF

Cyclohexyladenosine (CHA, 10^{-6}, 10^{-5}, 10^{-4} M) and cyclopentyltheophylline (CPT, 10^{-6} M) as a selective agonist and antogonist of adenosine A1 receptor had no significant effect on rCBF in sham operated, control and MDR (Fig .6).

Effects of CGS-21680 and ZM-241385 on rCBF

CGS-21680 (10^{-6} M) as selective adenosine A2a agonist increased rCBF in sham operated, control and MDR 15.97, 15.45 and 20.97 percent respectively so that the increase in rCBF in MDR was statistically significant (p<0.05). Effect of CGS-21680 (10^{-6} M) on rCBF inhibited by ZM-241385 (10-6 M), a selective adenosine A2a antagonist, although it alone has no significant effect on

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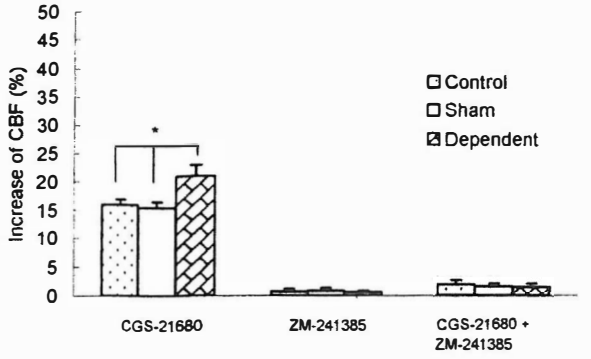

Fig. 7. Local effects of CGS-21680 (10^{-6} M), ZM-241385 (10^{-6} M) and CGS-21680 (10^{-6} M) + ZM-241385 (10^{-6} M) on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n =7). *p< 0.05, relative to control and sham operated animals.

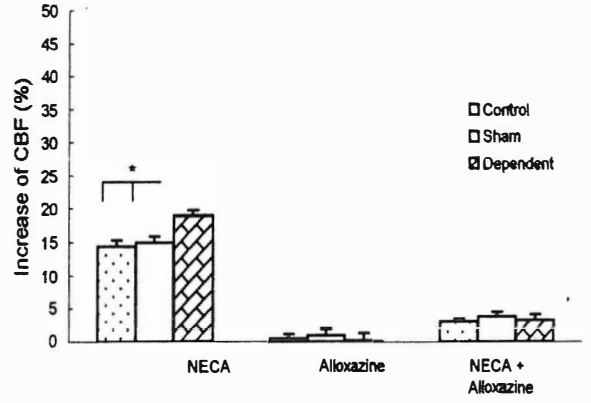

Fig. 8. Local effects of NECA (10^{-6} M), Alloxazine (10^{-6} M) and NECA (10^{-6} M) + Alloxazine (10^{-6} M), on rCBF in control, sham operated and MDR. Values are expressed as means ± S.E.M (n =7). *p<0.05, relative to control and sham operated animals.

CBF (Fig .7).

Effects of NECA and alloxazine on rCBF

NECA (10–6M) as a adenosine A2b agonist increased rCBF in sham operated, control and MDR 14.33, 14.91 and 18.88 percent respectively, so that the increase in rCBF in MDR was statistically significant (p<0.05). Alloxazine(10^{-6} M) as a selective adenosine A2b antagonist, inhibited the response to NECA (10^{-6} M), although it alone has no effect on rCBF (Fig .8).

Physiological parameters

Vital signs of the rats were recorded as follows: heart rate: 330 ±15 beat/min, systolic blood pressure: 102±3 mm Hg, diastolic blood pressure: 76±2.5 mm Hg, percent of arterial O_2 saturation: 94.9 ±0.75, PO_2: 78±3.5, PCO_2: 37.5±2.5, pH: 7.39 ± 0.15.

DISCUSSION

The results of this study indicated that adenosine (10^{-5}, 10^{-4}, 10^{-3}M) increases rCBF in the hind limb area of sensory cortex. The increase of rCBF in MDR was statistically significant in 10^{-4} and 10^{-3}M of adenosine (Fig. 3). These results show an increase in adenosine receptors responsiveness in MDR. This increase may be in adenosine receptors itself, or may be in one or several parts of intracellular signal transduction pathways. Adenosine's effect on rCBF was inhibited by theophylline (5×10^{-5}M), although it alone has no significant effect on rCBF, indicating that these responses are mediated by adenosine receptors and endogenous adenosine has no significant effect on rCBF (Fig. 4).

The specific adenosine receptors (P1 receptors) fall into various classes (A1, A2a, A2b and A3) with different functions.[16] Adenosine is an endogenous vasodilator considered to be involved in the local blood flow regulation of various tissues, such as the heart, brain and adipose tissue. This effect may be linked to the stimulation of adenylate cyclase and subsequent increase in smooth muscle cAMP, which is mediated through an adenosine receptor of the A2 subtype.[17] Adenosine induced vasodilation in the rat pial artery is mediated via activation of adenosine A2a and A2b receptors. Adenosine A2a receptors are linked to ATP-sensitive K+ channel, so that glibenclamide (K^+ channel blocker) reduces the response to A2a agonist (CGS-21680), and adenosine A2b receptors are coupled to the production of NO, so that the NO inhibitors (L-NAME) suppress the response to adenosine.[18] In this study therefore, the increase in adenosine responsiveness, seems to be due to increasing responsiveness of adenosine A2 receptors, although this does not exclude the changes in adenosine A1 receptors.

Adenosine is best known as an inhibitory neurotransmitter in the central nervous system. The inhibitory actions are most commonly mediated by the widespread A1 receptor which act via Gi to decrease cAMP levels and to decrease activation of Ca^{2+} channels and thereby reduce neurotransmitter release from central and peripheral neurons.[16] Therefore it is expected that adenosine decreases the neural metabolism through reducing neural activity. Neural activation and CBF are tightly coupled in both the resting and stimulated brain. Neural activity and CBF coupling is in fact so tight that it is used to study local neural activity by measuring rCBF or hemodynamics.[19] Therefore it could be expected that adenosine reduces the neural activity and metabolism by means

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of the A1 receptors and thereby reduces rCBF. But our results have shown an increase in CBF, therefore it is concluded that adenosine A1 receptors have no effects on rCBF functionally or that the dominant effects of adenosine A2 receptors on rCBF cover its effects. In order to eliminate probable effects of adenosine A1 receptors on cerebral metabolism and thereby the indirect effects on CBF, the next experiment was done. For this purpose 100 μL lidocaine (2%) was applied on cerebral cortex and thereafter adenosine (10^{-4} M) was used. Lidocaine decreased rCBF and following application of adenosine together with lidocaine increased rCBF. Although the response is higher in MDR, the difference between groups was not statistically significant (Fig .5). Also lidocaine reduced adenosine-induced increase in rCBF in three groups. Since lidocaine itself has different neural and vessel effects, it is difficult to describe these results. For example lidocaine as an antiarrhythmic agent (class I), inhibits Na^+, Ca^{2+} and K^+ channels. Class I antiarrhythmic drugs inhibit Ca^{2+} entry through voltage- and receptor-gated channels as well as Ca^{2+} release from intracellular stores. As a consequence, they decrease the availability of intracellular free Ca^{2+} required for vascular smooth muscle contraction and thereby decrease peripheral vascular resistance and arterial blood pressure.[20] It is expected that lidocaine with inhibition of Na^+ and Ca^{2+} channels in neurons, reduced neural metabolism and rCBF, but lidocaine has also vascular direct effects that interfere with it's neural effects. Lidocaine shows biphasic vascular effects in an in vivo rat microcirculatory preparation, with vasoconstriction occurring at low concentrations and relaxation at high concentrations. Lidocaine is capable of modifying the effects of both contractile and dilator agents in the vascular system, however the exact mechanisms of these direct vascular effects of lidocaine are not clear.[21]

In the next experiment, the effect of adenosine A1 receptor on rCBF was evaluated by using cyclohexyladenosine and cyclopentyltheophylline as a selective agonist and antagonist of the adenosine A1 receptor. Cyclohexyladenosine (10^{-6}, 10^{-5}, 10^{-4} M) and cyclopentyltheophylline (10^{-6} M) have no significant effect on rCBF in sham operated, control and MDR (Fig. 6). In this study adenosine A1 receptors have no significant effect on CBF in MDR, apparently indicating no change in A1 receptors. However the changes in adenosine A1 receptors in morphine dependency in other researches such as down regulation of adenosine A1 receptors in the nucleus tractus solitarius and spinal cord ,[11, 22] and up regulation of adenosine A1 receptors in whole brain homogenates and in the cortex in morphine dependent rats and mice[23,13] have been reported. According to our results, increase in adenosine responsiveness could be attributed to changes in adenosine A2 receptors. Therefore, in the next experiment, effects of adenosine A2 subtype receptors were evaluated by use of adenosine A2a and A2b agonists and antagonists. CGS-21680 (10^{-6}M) as a selective agonist of adenosine A2a receptors increased rCBF so that the responses were significant in MDR ($p<0.05$). These responses were inhibited by ZM-241385 (10^{-6} M), a selective adenosine A2b receptors antagonist, although it alone has no significant effect on CBF (Fig 7). Some researches indicated that among adenosine receptor agonists, NECA is the most potent agonist that activates the adenosine A2b receptor.[16,24] Therefore, NECA (10^{-6} M) was used as an adenosine A2b receptor agonist that increased rCBF so that the responses were significant in MDR($p<0.05$). These responses were inhibited by alloxazine (10^{-6} M), a selective adenosine A2b receptors antagonist, although it alone has no significant effect on CBF (Fig 8). So the use of CGS-21680 and NECA indicated that the increase in adenosine responsiveness in MDR could be due to an increase in adenosine A2a and A2b responsiveness. The changes of A2 receptors in morphine dependency had been reported in other experiments in different regions of the brain.[12,22] The probable reason of these changes may be because of decreased CBF in morphine dependency and this leads to a compensatory mechanism (increase in adenosine responsiveness) that returns CBF to normal values. In accordance with this idea, it has been reported that morphine decreased CBF so that the depressant effect of morphine in MDR was less than control animals; while naloxone had no considerable effect on CBF in control animals, it increased CBF in MDR.[15] Perhaps it could be concluded that morphine reduced the absolute amount of CBF in MDR and that naloxone reverses this effect.

In summary and according to the results of this study the involvement and increase in responsiveness of adenosine A2 receptors including A2a and A2b subtypes in MDR could be concluded. It is probable this increase in adenosine A2 receptor responsiveness, relatively returns CBF to normal values in morphine dependency. Furthermore in order to elucidate the exact mechanisms involved in this phenomenon the study of total CBF in MDR is suggested.

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