Intrathecal Adenosine Analog Administration Reduces Substance P in Cerebrospinal Fluid Along with Behavioral Effects That Suggest Antinociception in Rats

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Adenosine and adenosine analogs induce analgesia in humans and presumed antinociception in animal models when administered both systemically and intrathecally. In the present investigation in rats, we studied the effects of intrathecally administered adenosine analogs, with or without systemic coadministration of an adenosine antagonist (theophylline), on substance P (SP) and calcitonin gene-related peptide (CGRP) concentrations in cerebrospinal fluid (CSF). In parallel, nociceptive reflex testing (tail immersion latency) and motor function were evaluated. The potent unselective adenosine receptor agonist N-ethylcarboxamide-adenosine (NECA) and the relatively adenosine A₄ receptor selective agonist R-phenylisopropyl-adenosine (R-PIA) both reduced SP-like immunoreactivity (-LI) by 50%, whereas CGRP-LI remained unchanged. There was a dose-dependent increase in tail immersion latency. This effect was present without motor impairment when R-PIA was administered in doses up to 5 nmol. R-PIA (10–100 nmol), as well as 1–100 nmol of the unselective agonist NECA, produced dose-dependent motor impairment. The reduction of SP-LI as well as the behavioral effects were reversed by theophylline. We conclude that SP reduction in CSF, which possibly reflects reduced SP turnover after adenosine receptor stimulation, provides an additional possible mechanism of action for the analgesic effects of adenosine. Implications: We studied the interactions between the known pain mediator substance P and substances with effects similar to the endogenous pain modulator adenosine in rats. The results suggest that the pain-reducing effect of adenosine is, at least partly, due to a reduction of substance P in cerebrospinal fluid.

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A denosine is one of several endogenous compounds that have been attracting a growing interest concerning their role in nociception. Intravenous (IV), small-dose adenosine infusion in patients reduces postoperative pain and analgesic demand (1). Reduction of secondary hyperalgesia after cutaneous inflammation has also been shown (2). In patients suffering long-lasting, painful mononeuropathy with allodynia, symptoms of neuronal hyperexcitability were decreased by systemic infusion of adenosine (3). Intrathecal (IT) administration of the relatively adenosine A₁ receptor selective agonist R-phenylisopropyl-adenosine (R-PIA) provided long-lasting pain reduction in one patient suffering severe tactile allodynia (4).

In animal models for acute nociception, adenosine and its analogs have demonstrated inhibitory effects in nociceptive reflex tests (5). In rats with experimentally induced mononeuropathy (6), both systemic and IT administration of R-PIA reduced scratching and tactile hypersensitivity of the neuropathic hindlimb, which possibly reflects antinociception (7,8). The mechanisms of the analgetic effects of adenosine have been studied in animal models. Data indicate that the pain inhibitory effects are mediated via specific cell surface-associated adenosine A₁ receptors in the spinal cord dorsal horn (5,9). Adenosine A₁ receptors in the spinal cord are linked to the inhibition of adenyl cyclase activity (5). In neurophysiological studies, adenosine inhibited synaptic transmission in the substantia gelatinosa of the spinal cord dorsal horn via hyperpolarization of the postsynaptic membrane (10). A presynaptic action via Ca²⁺ current inhibition has also been suggested (5,10). Another possible spinal mechanism is that the inhibitory effects of adenosine are potentiated by tachykinins (11,12). Using in
vitro models, interaction between substance P (SP) and adenosine with respect to changes in tachykinin receptor binding (13), and adenosine-mediated inhibition of the release of SP as well as calcitonin gene-related peptide (CGRP) from capsaicin-sensitive primary afferents in the rat dorsal horn has been shown (14).

The transmission and modulation of nociceptive input in the dorsal horn of the spinal cord is a most complex process in which several neurotransmitters have been implicated (15). Among the endogenous peptides shown to play a central role are SP and CGRP. Colocalized with excitatory amino acids in small diameter primary afferent neurons, they facilitate the transmission of nociceptive input (15). The C-fiber release of SP and excitatory amino acids after noxious stimulation is reduced by exogenous opioids, and IT administration of SP antagonists also inhibits presumed pain behavior in animal models (15). CGRP is also released in the dorsal horn after noxious stimuli (15). A possible effect of CGRP is that by inhibiting the endopeptidases responsible for peptide degradation, it may increase the spread and, thereby, the effects of SP (16).

The aim of this study was to investigate the effect of adenosine receptor stimulation on the concentrations of SP-like immunoreactivity (-LI) and CGRP-LI in cerebrospinal fluid (CSF) in rats. We also set out to study the effects on a behavioral parameter with possible relevance to nociception (tail immersion latency) as well as motor function. Further, the effect of systemic coadministration of an adenosine antagonist (theophylline) was evaluated.

Methods

All experiments were performed with the approval of the local animal ethics committee. The experimental protocol was divided into four parts (I–IV), as illustrated in Table 1. Male Sprague-Dawley rats (ALAB, Sollentuna, Sweden) weighing 250–280 g were used for Parts I–III. In Part IV, a similar but not identical strain of male rats (SD, also from ALAB) was used, because the breeder at this time had modified its strain of rats and could no longer deliver animals identical to those used in Parts I–III. All treatment procedures were performed by an investigator blinded to the intervention.

Part I

The animals were anesthetized for surgery by intraperitoneal injection of 350 mg/kg chloral hydrate (KEBO, Spånga, Sweden). A catheter (PE 10, outer diameter 0.61 mm) was inserted through the atlantooccipital membrane into the spinal subarachnoid space, with the tip in the lumbar region (17). The animals were allowed 7 days for recovery and showed no signs of spinal cord injury. The rats were kept in separate cages with free access to food and water. Two days after surgery, the IT position of the catheter was confirmed by the injection of 7 µL of lidocaine (50 mg/mL, Xylocaine; Astra, Södertälje, Sweden) followed by 15 µL of saline. This produced a temporary paralysis of the hindlimbs. The catheter was used for all IT drug administration but not for aspiration of CSF in these animals.

Parts II–IV

A simpler procedure for IT drug administration in alert animals was used in these parts (18). Drugs were injected IT using a stainless steel 26-gauge cannula inserted directly into the subarachnoid space between the third and fourth, or fourth and fifth, lumbar vertebrae. The IT position was confirmed by the occurrence of a tail flick. Systemic drugs (theophylline 50 mg/kg or saline) were administered IV via a tail vein using a 26-gauge cannula.

Drugs, Peptide Analyses, and Behavioral Studies

All IT drugs were administered in a volume of 10 µL (followed by 15 µL of saline when an implanted IT catheter was used). The adenosine receptor antagonist and agonists used were theophylline 20 mg/mL (ACO, Stockholm, Sweden), R-PIA (Boehringer-Mannheim Biochemica, Ingelheim, Germany), N-ethylcarboxamidoadenosine (NECA; Astra). Because of its limited solubility in water, R-PIA was dissolved in hydrochloric acid and then buffered to a pH of 7.0 using sodium hydroxide. The solution was then diluted in saline to the required concentration in each case.

CSF SP-LI and CGRP-LI were analyzed using radioimmunoassay methods. For SP-LI antiserum-SP2, which reacts equally with SP and SP-sulfoxide but not with other tachykinins, was used. Intrar- and interassay coefficients of variation were 7% and 11%, respectively (19). CGRP-LI was analyzed using antiserum-CGRP88. High-performance liquid chromatography-purified 125-Histidyl rat CGRP was used as radioligand.

### Table 1. Experimental Schedule

<table>
<thead>
<tr>
<th>Part</th>
<th>X</th>
<th>O</th>
<th>△</th>
<th>£</th>
<th>□</th>
<th>▲</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part I</td>
<td>X</td>
<td>O</td>
<td>△</td>
<td>£</td>
<td>□</td>
<td>▲</td>
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<tr>
<td>Part II</td>
<td>O</td>
<td>△</td>
<td>▲</td>
<td>□</td>
<td>△</td>
<td>£</td>
</tr>
<tr>
<td>Parts III and IV</td>
<td>△</td>
<td>□</td>
<td>▲</td>
<td>£</td>
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</tr>
</tbody>
</table>

Explanation:
- X = implantation of IT catheter
- O = IT drug administration
- △ = IV injection of theophylline/saline
- £ = motor score evaluation
- □ = tail immersion latency evaluation
- ▲ = aspiration of CSF

IT = Intrathecal, IV = Intravenous, CSF = Cerebrospinal fluid.
Table 2. CSF SP-LI and CGRP-LI Concentrations in Parts II–IV

<table>
<thead>
<tr>
<th>IT drug</th>
<th>Part II</th>
<th></th>
<th>Part III</th>
<th></th>
<th>Part IV</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP-LI</td>
<td>CGRP-LI</td>
<td>SP-LI</td>
<td>CGRP-LI</td>
<td>SP-LI</td>
<td>CGRP-LI</td>
</tr>
<tr>
<td>Saline</td>
<td>53.5 ± 13.6</td>
<td>21.2 ± 8.3</td>
<td>61.4 ± 14.0</td>
<td>22.3 ± 8.5</td>
<td>65.6 ± 15.4</td>
<td>28.8 ± 17.4</td>
</tr>
<tr>
<td>R-PIA 1 nmol</td>
<td>56.8 ± 13.6</td>
<td>27.5 ± 6.3</td>
<td>58.4 ± 28.7</td>
<td>32.5 ± 17.6</td>
<td>59.0 ± 17.6</td>
<td>30.6 ± 10.3</td>
</tr>
<tr>
<td>R-PIA 5 nmol</td>
<td>53.9 ± 18.5</td>
<td>30.3 ± 11.5</td>
<td>30.9 ± 11.6t</td>
<td>22.7 ± 10.5</td>
<td>42.1 ± 13.8t</td>
<td>20.8 ± 5.9</td>
</tr>
<tr>
<td>R-PIA 10 nmol</td>
<td>30.5 ± 11.9*</td>
<td>27.4 ± 9.2</td>
<td>52.0 ± 10.2</td>
<td>24.9 ± 4.6</td>
<td>63.0 ± 10.2</td>
<td>24.5 ± 13.0</td>
</tr>
<tr>
<td>NECA 1 nmol</td>
<td>53.2 ± 14.2</td>
<td>25.4 ± 10.4</td>
<td>31.0 ± 12.3*</td>
<td>21.3 ± 8.3</td>
<td>43.4 ± 16.2*</td>
<td>28.8 ± 9.6</td>
</tr>
<tr>
<td>NECA 5 nmol</td>
<td>43.2 ± 19.0</td>
<td>27.9 ± 19.1</td>
<td>58.4 ± 14.7</td>
<td>21.6 ± 9.9</td>
<td>55.0 ± 11.4</td>
<td>23.5 ± 11.9</td>
</tr>
<tr>
<td>NECA 10 nmol</td>
<td>27.6 ± 13.4+</td>
<td>19.8 ± 10.4</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Data are mean ± SD.

IT = intrathecal, SP-LI = substance P-like immunoreactivity, CGRP-LI = calcitonin gene-related peptide-like immunoreactivity, R-PIA = R-phenylisopropyl-adenosine, NECA = N-ethylcarboxamide-adenosine, theo = theophylline.

Cross-reactivity toward rat CGRP I and II was 100% and 120%, respectively. Intra- and interassay coefficients of variation were 8% and 14%, respectively (20).

All behavioral tests were performed by the same investigator. Tail immersion latency was tested as described by Woolf et al. (21). Cut of time was 15 s. Motor score was evaluated using the method described by Karlsten et al. (22), using four grades: 1 = no motor impairment, 2 = partial paresis of the hindlimbs, 3 = full paresis of the hindlimbs, 4 = full paresis of the hindlimbs and some impairment in the front limbs.

Experimental Schedule

Part I. These animals (n = 6–8 per group) were used to study the effect on tail immersion latency and motor score after the IT injection of 1, 5, 10, 30 or 100 nmol of R-PIA via the implanted catheter (NECA was not used in this part of the study). These behavioral variables were assessed repeatedly during the 90 min after injection (see Table 1).

Part II. This part (n = 7–8 per group) was designed to analyze the CSF concentrations of SP-LI and CGRP-LI after the IT administration of 1, 5, or 10 nmol of R-PIA and NECA, respectively. Saline was used as control. Using the time of IT drug administration as the starting point, tail immersion latency and motor score tests were performed at 30 min. Sixty minutes after IT drug administration, the animals were anesthetized with intraperitoneal chloral hydrate. A 26-gauge steel cannula was used to stereotactically cannulate the fourth ventricle (20). CSF was aspirated (up to 200 μL or until blood appeared in the cannula). The animals were then killed. CSF SP-LI and CGRP-LI were analyzed.

Part III. The reversibility of the effects found in Part II were tested. The adenosine antagonist theophylline (50 mg/kg) or an equal volume of saline was injected IV 5 min after the IT injection of 10 nmol of R-PIA, NECA, or saline (n = 7–10 per group). The time of administration of the adenosine antagonist was chosen to produce high serum concentrations in the time interval when maximal antinociceptive effects of R-HA and NECA have been shown to occur (22) and still leave the animal time to recover from the IV injection before behavioral assessment (25 min). The schedule for behavioral assessments and peptide analyses were the same as those in Part II.

Part IV. This part consisted of tests similar to those in Part III, but they were performed on a modified strain of rats (n = 8 per group), and they used 10 or 30 nmol of R-PIA, NECA, or saline IT in combination with systemic theophylline or saline, as described above.

Statistics

Motor score results are shown as median and quartiles. All other results are shown as mean ± so. The Mann-Whitney U-test was used in all statistical evaluations. P values <0.05 were considered significant. In Part I, the results from all the saline-treated animals used in Parts II and III (n = 26) were used as control group (control animals from Part IV were excluded because they were of a slightly different strain). In all other parts, the results were compared with the saline-treated animals in the same part of the study.

Results

The CSF concentrations of SP-LI and CGRP-LI are shown in Table 2. The concentration of SP-LI in CSF was significantly reduced in both R-PIA- and NECA-treated animals. When Sprague-Dawley rats were used, this effect was significant after 10 nmol of R-PIA or NECA. In the SD rats used in Part IV, the reduction was significant after 30 nmol but not after 10 nmol.
Coadministration of theophylline abolished the reduction of SP-LI. No statistically significant differences in the CSF concentration of CGRP-LI were found in any group of animals.

The results of the behavioral assessments of Part I (IT R-PIA, 1-100 nmol) are shown in Figure 1, and the results from Part III (10 nmol of R-PIA or NECA with or without systemic theophylline) are shown in Table 3. The Sprague-Dawley rats had behavioral test results similar to those of SD strain when saline-treated animals were compared (data not shown). All doses of NECA (1-100 nmol) and the larger doses of R-PIA (10-100 nmol) caused motor deficiencies with long onset latency and duration that outlasted the observation period. In Part II, the motor score 30 min after the IT injection of 1, 5, or 10 nmol of R-PIA was normal (Grade 1) in all animals, whereas the same doses of NECA resulted in median motor scores of 1 (1-1.5), 1.5 (1-2.5) \( (P < 0.05), \) and 3.5 (3-4) \( (P < 0.01)\).

The increase in tail immersion latency after both R-PIA and NECA administration was dose-dependent. The prolongation of tail immersion latency had a shorter onset latency and duration than the motor effects discussed above. IV theophylline alone shortened the tail immersion latency, and when it was combined with IT adenosine analogs, the changes in motor performance and tail immersion latency were either blocked or markedly attenuated.

The results of the behavioral as well as peptide-LI tests were consistent throughout all parts of the study. The results of some measurements in some groups are not shown because they add no further information.

### Discussion

The major novel finding of this study is that SP-LI, but not CGRP-LI, is reduced in CSF in neurologically intact rats after the IT administration of adenosine analogs. This effect was seen regardless of whether the IT administered drug was a nonselective (NECA) or adenosine A1 receptor-selective agonist (R-PIA). In addition, the changes in an acute nociceptive threshold test (tail immersion latency) suggest antinociception. Changes in both behavioral and CSF neuropeptide-LI concentrations after adenosine receptor stimulation were antagonized by the systemic administration of an adenosine receptor antagonist (theophylline). In fact, theophylline treatment alone induced significant hyperreactivity in the tail immersion test. The mechanism for this response may involve loss of modulation of nociception by endogenous adenosine, but possibly also involves other unrelated effects of theophylline (23).

The site of action for the observed behavioral as well as neurochemical effects could involve spinal and supraspinal mechanisms. The SP-LI and CGRP-LI are found in sensory neurons in the dorsal horn and also within the brain, primarily in striatonigral pathways, the hypothalamus, and the limbic forebrain (24). A supraspinal spread and effect of spinally administered adenosine analogs is possible. Such supraspinal sites of

### Table 3. Behavioral Data in Part III

<table>
<thead>
<tr>
<th>IT Drug + systemic drug</th>
<th>Motor score*</th>
<th>Tail immersion latency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + saline</td>
<td>1 (1-1)</td>
<td>4.6 ± 1.8</td>
</tr>
<tr>
<td>Saline + theo</td>
<td>1 (1-1)</td>
<td>3.0 ± 1.4*</td>
</tr>
<tr>
<td>R-PIA 10 nmol + saline</td>
<td>1 (1-1)</td>
<td>12.0 ± 3.1†</td>
</tr>
<tr>
<td>R-PIA 10 nmol + theo</td>
<td>1 (1-1)</td>
<td>3.7 ± 0.8</td>
</tr>
<tr>
<td>NECA 10 nmol + saline</td>
<td>4 (2.25-4.0)†</td>
<td>8.4 ± 2.6†</td>
</tr>
<tr>
<td>NECA 10 nmol + theo</td>
<td>1 (1-2)</td>
<td>3.8 ± 1.5</td>
</tr>
</tbody>
</table>

* \( P < 0.05, \) † \( P < 0.01. \)

* Motor score grade (median and quartiles) and tail immersion latency in seconds (mean ± sd) 30 min after intrathecal (IT) injection.

R-PIA = R-phenylisopropyl-adenosine, NECA = N-ethylcarboxamide-adenosine, theo = theophylline.
action could be reached either by rostral spread in the CSF or, although less likely, via the systemic circulation. Because the adenosine analogs were administered at a lumbar spinal level, and based on earlier studies, we primarily discuss possible interactions on the spinal cord level. The preferential paraparesis after both NECA and the larger doses of R-PIA also indicate major distribution at the spinal cord level.

The reduction by half of the SP-LI concentration in CSF after IT adenosine analog administration indicates that SP turnover, involving both inhibition of SP release and increased elimination, is altered in the central nervous system. This reduction of SP could be of importance for the changes in tail immersion latency, which suggest algnesia. The changes in SP-LI were found when doses of adenosine analogs larger than those needed to induce detectable tail immersion latency changes, were administered. It is also noteworthy that the obvious dose-dependence of the changes in motor performance and acute nociceptive reflex testing could not be shown when SP-LI was evaluated. It is possible that local changes in SP in the spinal cord, involved in the observed modulation of the response to nociceptive stimulation, occur without significant changes in the concentration of SP-LI in the CSF collected. Evidence to support this may be gathered by direct measurements of spinal cord peptide content. CSF was collected 60 minutes after the IT injection of the adenosine agonist, when a presumed analgetic effect was still present but when little or no motor impairment was observed as an effect of R-PIA in the doses that produced a significant SP-LI reduction. This suggests that the peptides in CSF at this time reflected neuronal release during the interval when R-PIA produced antinociception but mild or nonexistent motor impairment. The difference in SP-LI levels found when SD rats were used might be explained by the use of a modified strain of animals, which possibly reflects differences in sensitivity to adenosine receptor stimulation.

The mechanism of action for the demonstrated adenosine receptor-mediated reduction of SP-LI and its relevance to antinociception remains speculative. Some information about the influence of adenosine on SP and CGRP release from the spinal cord is available. As judged from in vitro data on rat spinal cord slices (after chronic nerve damage), adenosine and its analogs fail to antagonize stimulated SP release (25). However, this finding does not rule out the possibility that adenosine receptor stimulation modifies the SP turnover in intact animals. The CSF concentration of CGRP-LI remained unchanged in all groups of the present study in which CSF was analyzed, which indicates that adenosine does not affect CGRP turnover in the unchallenged intact nervous system. This finding is also in contrast to an in vitro study by Santicioli et al. (14), in which adenosine-induced inhibition of the release of both CGRP and SP from capsaicin-sensitive primary afferent terminals in the rat dorsal horn was shown. The differences could be explained by the use of in vitro models instead of intact animals, as used in the present study, in which both ascending and descending pathways are intact and may influence the overall response to adenosine receptor stimulation. Different anatomical sites of sample collection could also account for this difference.

Dorsal horn SP, released by noxious but not by nonnoxious stimuli, originates from primary afferent, intrinsic, and descending spinal cord neurons (15,26). The role of SP in hyperalgesia and neuronal hyperexcitability has been extensively studied (27). Numerous reports also suggest the involvement of CGRP in spinal cord transmission of nociception (cf. 15), but the role of CGRP is not as well studied as that of SP due to a shortage of selective antagonists.

The finding of changes in SP-LI but not CGRP-LI concentrations in CSF after IT adenosine analog administration indicates a selective rather than a general inhibitory effect of adenosine receptor stimulation. Both similarities and differences with other aspects of spinal cord modulation of nociception can be found in the results of the present study. The adenosine receptor-mediated reduction of CSF SP-LI, but not of CGRP-LI levels, shows a similarity with the y-aminobutyric acid (GABA) system. In chronic monoarthritic rats, the GABAergic receptor antagonist (GFP 36742) was shown to enhance SP release, whereas CGRP was unaffected (28). This suggests the tonic inhibitory effect on spinal SP turnover mediated via GABAergic receptors. This proposed inhibition of SP but not CGRP release by both GABA- and adenosine-mediated mechanisms is in contrast to the action of endogenous opioids, because naloxone enhanced both SP and CGRP release in the same chronic pain model (28). However, it should be noted that the model using intact animals in the present study is different from the above-referenced studies using monoarthritic rats.

The dose-dependent increase in tail immersion latency after adenosine analog administration has a much earlier onset and different duration than the motor deficit seen in animals after IT NECA and larger doses of IT R-PIA. When these motor deficits do occur, they do not seem to increase tail immersion latency, which suggests that this sacral segment nociceptive reflex test is little affected by the loss of motor function.
at the lumbar level. This study confirms the results of
a previous study (22) that shows these dose-
dependent effects and the duration of IT administra-
tion of adenosine receptor agonists with regard to
acute nociceptive threshold testing and motor func-
tion. The observed differences in behavioral effects
after administration of the relatively adenosine A1
receptor-selective agonist R-PIA and the potent but
nonselective agonist NECA are well known (23). Be-
cause no adenosine A2 receptor-selective agonists or
unselective antagonists was used, the observed effects
could be adenosine A1 receptor- and/or adenosine A2
receptor-mediated. The observed differences could
also be caused by variable penetration times into dif-
ferent parts of the spinal cord, as well as the result of
involvement of different adenosine receptors, as pre-
viously discussed (22).

In conclusion, IT adenosine receptor agonist treat-
ment reduces SP-LI levels in CSF and causes dose-
dependent behavioral effects, which suggest antino-
ception. This novel interaction between adenosine
receptor stimulation and SP turnover warrants further
evaluation of adenosine agonist action on spinal cord
 modulation of nociception.

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References

1. Segerdahl M, Ekblom A, Sandelin K, et al. Peroperative ade-
osine infusion reduces the requirements for isoflurane and post-
attenuates touch evoked allodynia induced by mustard oil in
infusion alleviates spontaneous and stimulus evoked pain in
patients with peripheral neuropathic pain. Anesth Analg 1995;
ishes allodynia elicited by vibration and touch after intrathecal
5. Sawynok J, Sweeney MI. The role of purines in nociception.
6. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that
produces disorders of pain sensation like those seen in man.
7. Sjölund K-F, Sollevi A, Segerdahl M, et al. Intrathecal and
systemic R-phenylisopropyladenosine reduces scratching be-
aviour in a rat mononeuropathy model. Neuroreport 1996;7:
1856–60.
receptor activation suppresses tactile hypersensitivity and po-
tentiates spinal cord stimulation in mononeuropathic rats. Neu-
9. Poon A, Sawynok J. Antinociception by adenosine analogs and
an adenosine kinase inhibitor: dependence on formalin concen-
10. Li J, Perl ER. Adenosine inhibition of synaptic transmission in
11. Salter MW, De Koninck Y, Henry JL. Physiological roles for
adenosine and ATP in synaptic transmission in the spinal dorsal
12. De Koninck Y, Salter MW, Henry LH. Substance P released
endogenously by high-intensity sensory stimulus potentiates
purinergic inhibition of nociceptive dorsal horn neurons in-
13. Stiller CO, Faisbom J, Fredholm BB, Brodin E. The adenosine
analogue R-PIA interacts with substance P binding in rat brain
14. Santilli P, Del Bianco E, Tramontana M, Maggi CA. Adeno-
sine inhibits action potential-dependent release of calcitonin
gene-related peptide- and substance P-like immunoreactivities
from primary afferent in rat spinal cord. Neurosci Lett 1992;
144:211–4.
16. Schaible HG, Hoppe PF, Lang CW, Duggan AW. Calcitonin gene-
related peptide causes intraspin al spreading of substance P
17. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal
18. Yu LC, Hansson P, Lundeberg T. Opioid antagonists naloxone,
ß-funaltrexamine and naltrindole, but not nor-binaltorphimine,
reverse the increased hindpaw withdrawal latency in rats in-
duced by intrathecal administration of the calcitonin gene-
city in rat central nervous system as studied using antisera raised
20. Bileviciute J, Lundeberg T, Ekblom A, Theodosiou E. Sub-
stance P-, neurokinin A-, calcitonin gene-related peptide- and
neuropeptide Y-like immunoreactivities (LI) in rat knee joint
synovial fluid during acute monoarthritis is not correlated with
concentrations of neuropeptide-LI in cerebrospinal fluid and
21. Woolf CJ, Mitchell D, Barrett GO. Antinociceptive effect of
injection of the adenosine receptor agonist R-phenylisopropyl-
adenosine and N-ethylcarboxamide-adenosine on nocicep-
23. Paalzow GHHM. Noradrenaline but not dopamine involved in
NMDA receptor-mediated hyperalgesia induced by thio-
24. Iversen LL. Central actions of substance P and related tachy-
25. Vasko MR, Ono H. Adenosine analogs do not inhibit the
potassium-stimulated release of substance P from rat spinal
cord slices. Naunyn Schmiedebergs Arch Pharmaco1990;342:
411–6.
substance P, vasoactive intestinal polypeptide, cholecystokinin,
neurotensin, Met-enkephalin, bombesin and PHI in the spinal
27. Traub RJ. The spinal contribution of substance P to the gener-
atation and maintenance of inflammatory hyperalgesia in the rat.
28. Malcangio M, Bowery NG. Calcitonin gene-related peptide con-
tent, basal outflow and electrophysically-evoked release from mono-