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Tolbutamide blocks postsynaptic but not presynaptic effects of adenosine on hippocampal CA1 neurones

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Summary. Extracellular recording in the CA1 pyramidal cell layer of rat hippocampal slices was used to examine the effect of the ATP-sensitive potassium channel blocker tolbutamide and the channel opener levcromakalim on responses to adenosine. Tolbutamide 1 mM blocked the inhibitory effect of adenosine on the size of orthodromic population spikes but had no effect on the inhibitory action of adenosine on field EPSPs. Tolbutamide also blocked the suppression by adenosine of repetitive antidromic spikes induced in calcium-free media with high magnesium but did not prevent the effects of baclofen. Levcromakalim 100 μM potentiated inhibitory effect of adenosine, but not baclofen, on orthodromic population spikes. The results show that at postsynaptic, but not presynaptic, sites adenosine may activate an ATP-sensitive potassium channel.

Keywords: Adenosine, baclofen, ATP-sensitive potassium channel (K_{ATP}), tolbutamide, levcromakalim, rat hippocampus.

Introduction

Adenosine actions may be mediated pre- and postsynaptically through receptor-mediated mechanisms including effects on second messenger systems, transmembrane ion fluxes and neurotransmitter release (Stone and Simmonds, 1991). At presynaptic sites, adenosine decreases the release of different neurotransmitters such as glutamate (Fastbom and Fredholm, 1985), acetylcholine (Jackisch et al., 1984; Spignoli et al., 1984) and monoamines (Michaelis et al., 1979; Feuerstein et al., 1985) while postsynaptically it hyperpolarizes neurones via activation of potassium channels (Greene and Haas, 1985; Trussel and Jackson, 1985). Baclofen, a $GABA_B$ agonist, can also act presynaptically to reduce transmitter release or postsynaptically to hyperpo-

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larize hippocampal pyramidal cells by an increase in potassium conductance (Gahwiler and Brown, 1985).

In the CNS, the type of potassium channel activated by adenosine is unclear. Barium can block the adenosine- (Thompson et al., 1992) and baclofen- (Gahwiler and Brown, 1985) activated potassium conductance in the rat hippocampus but barium is a non-selective potassium channel blocker and can block several K^+ currents such as I_K, I_{KATP} and I_M (Cook, 1988). Gerber et al., (1989) reported that adenosine had no effect on a 4-aminopyridine (4-AP) sensitive transient (I_A) and tetraethylammonium (TEA) sensitive delayed (I_K) outward currents on hippocampal neurones, but in several areas of brain including the hippocampus (Schubert and Lee, 1986), cerebral cortex (Perkins and Stone, 1980), olfactory cortex (Scholfield and Steel, 1988) and locus coeruleus (Pan et al., 1994) it has been reported that adenosine may activate I_A. Recently Li and Henry (1992) reported that adenosine-induced hyperpolarization was depressed by glibenclamide, a blocker of ATP-sensitive K^+ channels, in rat CA1 neurones. We have now examined the effect of tolbutamide, a K_{ATP} blocker and levcromakalim, a K_{ATP} opener on responses to adenosine to determine whether adenosine may activate K_{ATP} channels presynaptically as well as postsynaptically and whether these channels are involved in the potent suppression by adenosine of repetitive spikes induced by low calcium medium (Lee et al., 1984).

Methods and materials

Male Wistar rats (170–210 g) were anaesthetized with urethane (1.3 g/kg. I.P.) and decapitated. The brains were rapidly taken out and put in ice-cold artificial cerebrospinal fluid (ACSF) with the following composition (mM):NaCl 115, KH_2PO_4 2.2, KCl 2.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25 and glucose 10. The hippocampi were cut transversely into 450 μm thick slices using a McIlwain tissue chopper. The slices were kept in an incubation chamber containing an ACSF-saturated atmosphere of 95% O_2 and 5% CO_2 at room temperature for at least one hour before using. Individual slices were then transferred to a one ml capacity recording chamber and superfused with ACSF at 30°C ± 0.5, gassed with the O_2/CO_2 mixture to yield pH of 7.4. The slices were completely submerged in the medium which was superfused continuously at a rate of about 4 ml/min. Although concern is occasionally expressed about the degree of hypoxia present in the middle regions of these slices, measurements of adenosine release from slices of around 400 μm thickness in vitro have indicated levels of less than 1 μM (Lloyd et al., 1993). Since applied adenosine does not have significant effects at concentrations less than about 5 μM, it is unlikely that hypoxically induced release could have affected the sensitivity of slices or their behaviour in this study.

We have employed three recording paradigms to distinguish presynaptic and postsynaptic effects of adenosine in this study. The recording of orthodromically evoked population spikes provides an indication of postsynaptic excitability, although this is susceptible to changes secondary to an alteration of transmitter release. The latter can be estimated by recording the field excitatory postsynaptic potential (EPSP). Conversely, a relatively direct measure of postsynaptic changes is afforded by an examination of the antridromically evoked action potential, especially when postsynaptic excitability is enhanced by procedures such as that adopted here of lowering extracellular calcium levels.

Adenosine and baclofen were applied for 10 minutes. Tolbutamide and levcromakalim (BRL 38227) were applied before adenosine or baclofen for 15 minutes. In antidromic stimulation experiments, $CaCl_2$ was omitted and $MgSO_4$ increased to 4 mM.

After orthodromic stimulation of Schaffer collateral fibres in stratum radiatum near the border of CA2–CA3, recordings were made in the CA1 pyramidal cell layer or the stratum radiatum for population spikes or field EPSPs (fEPSPs) respectively. Stimulation of the alveus by a concentric bipolar electrode was used to induce antidromic invasion of CA1 cells. Pulses of 0.1 ms duration and 100–500 μA amplitude were delivered every 60 seconds. For orthodromic fEPSPs the duration of the stimulus was decreased to 20–50 μs. Recordings were made with 2–4 μm diameter glass microelectrodes containing 2 M NaCl. The recorded signals were amplified and displayed on storage oscilloscopes and then plotted on a chart recorder. Stimulus strength was adjusted to reduce the orthodromic population spike (P.S.), fEPSPs or the secondary spike (S.S.) of a burst induced by antidromic stimulation to 75% of maximum to avoid supramaximal responses. Increases or decreases in the potential size induced by tolbutamide or levcromakalim were negated by adjusting the stimulus so as to restore the potential to its control size. The size of the orthodromic population spike and antidromic secondary spike were measured as the peak to peak amplitudes. The size of fEPSPs was measured between the negative going peak and the base line of stimulation. Results are presented as mean ± s.e.m. for n experiments, and the statistical significance of any difference was assessed by Student's t-test. Differences were considered significant with $p < 0.05$. Tolbutamide and levcromakalim were dissolved in DMSO. Control experiments showed that DMSO itself had no effect on the slice at concentrations up to 0.1%. Other chemical agents were dissolved in normal ACSF or calcium-free medium (containing 4 mM magnesium). All agents were obtained from Sigma chemical company except levcromakalim which was from SmithKline Beecham pharmaceuticals.

Results

Orthodromic stimulation

Adenosine at 5 and 10 μM reduced the amplitude of orthodromic population spikes by 27.7% ± 2.6 ($P < 0.01$, $n = 4$) and 42.4% ± 1.8 ($P < 0.001$, $n = 4$) respectively. The depressant effect of adenosine was quickly and readily reversible and washed out in less than 5 minutes. Tolbutamide alone at 1 mM increased the population spike size by 6.89% ± 4.07 (n.s., $n = 3$) and 12.48% ± 3.81 ($n = 4$, $P < 0.05$) respectively. This effect developed over about 5 minutes. Tolbutamide at 1 mM decreased the effect of ade–nosine by about 50% at both of the purine concentrations examined, though the reduction was statistically significant with only the 10 μM level (Fig. 1).

Levcromakalim, 100 μM had no significant effect itself on orthodromic population spike size but it reversibly potentiated the inhibitory effect of adenosine on the potential size (Fig. 2). In contrast, levcromakalim 100 μM did not change the inhibitory effect of baclofen applied at 1 or 2 μM (Fig. 3).

Baclofen at 1 and 2 μM reduced the amplitude of population spikes by 14.2% ± 1.02 ($n = 4$, $P < 0.001$) and 38.9% ± 4.26 ($n = 4$, $P < 0.01$) respectively. Tolbutamide (1 mM) itself increased the size of potential by 8.91% ± 2.73 ($P < 0.05$, $n = 4$) but had no significant effect on the inhibitory action of baclofen 1 μM and 2 μM ($n = 4$) (Fig. 4).

Adenosine at 10 and 20 μM decreased the size of the field EPSPs by 11.21% ± 2.65 ($n = 4$, $P < 0.05$) and 34.13% ± 1.21 ($n = 4$, $P < 0.001$) respectively. Tolbutamide, 1 mM did not affect this presynaptic effect of adenosine at either concentration ($n = 4$, Fig. 5).

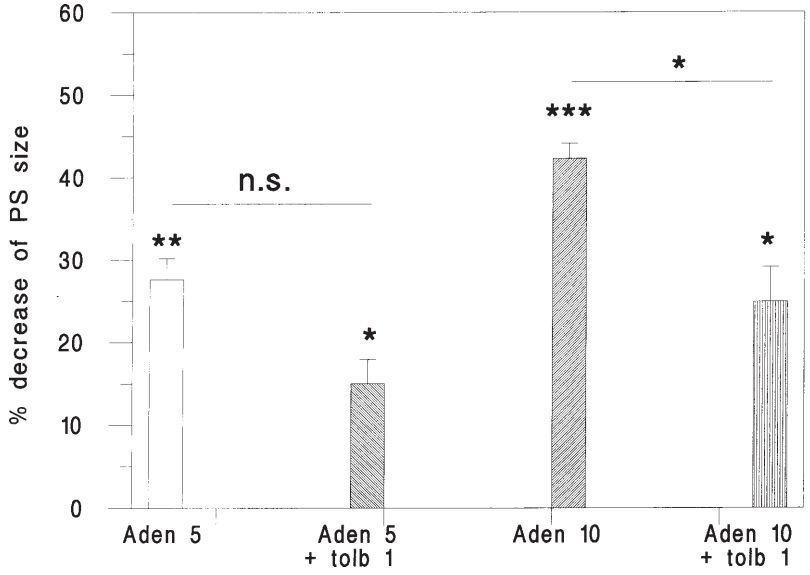

Fig. 1. Histogram showing the effect of adenosine (Aden) 5 and 10 μM and tolbutamide (tolb) 1 mM on orthodromically evoked CA1 population spikes (PS). Each vertical bar represents the mean ± s.e.m. for n = 4 slices. Student's t test was employed to determine the significance level relative to control potentials or to adenosine alone as indicated (*P < 0.05; **P < 0.01; ***P < 0.001)

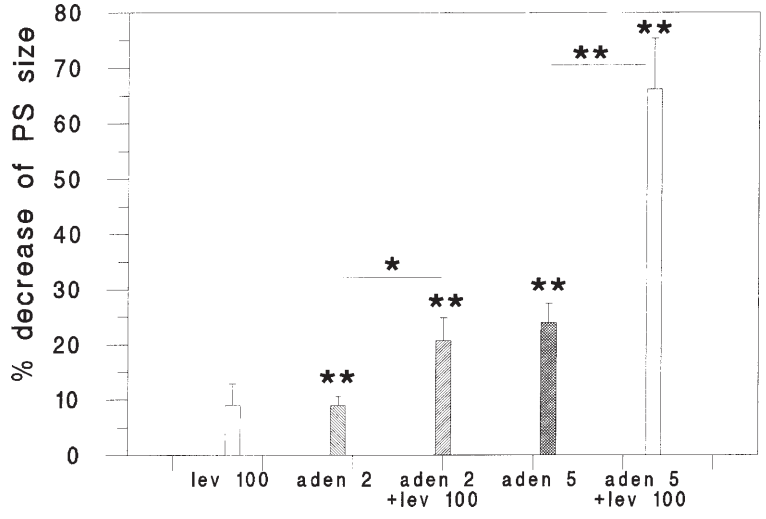

Fig. 2. Histogram showing the effect of adenosine (aden) 2 and 5 μM and levcromakalim (lev) 100 μM on orthodromically evoked CA1 population spikes (PS). Each vertical bar represents the mean ± s.e.m. for n = 4. Student's t test was employed to determine the significance level (*P < 0.05; **P < 0.01; ***P < 0.001). *n.s.* non significant

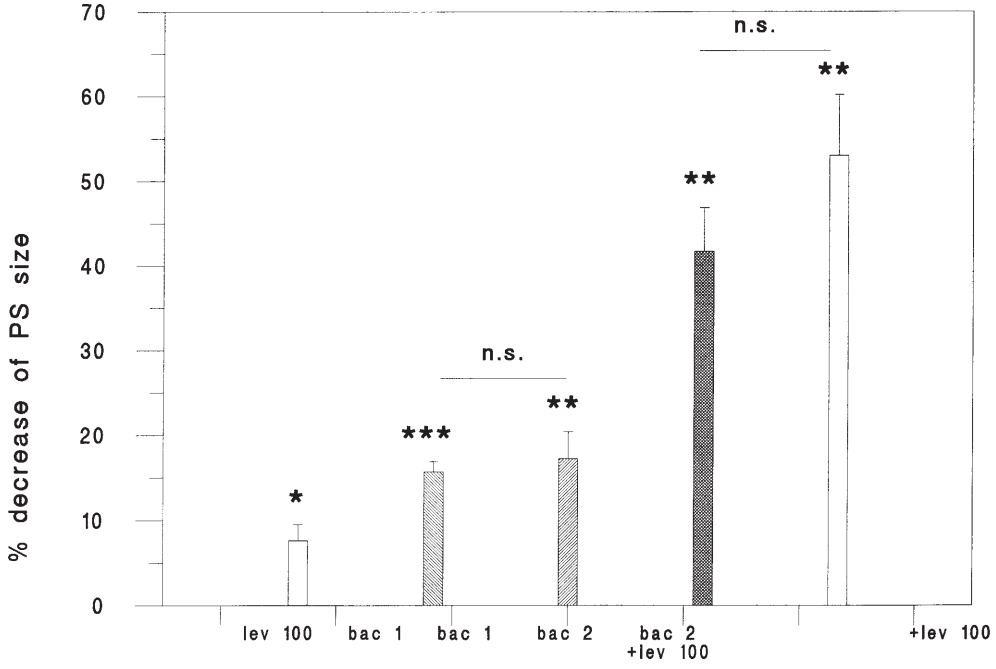

Fig. 3. Histogram showing the effect of baclofen (bac) 1 and 2 μM and levcromakalim (lev) 100 μM on orthodromically evoked CA1 population spikes (PS). Each vertical bar represents the mean ± s.e.m. for n = 4. Student's t test was employed to determine the significance level (*P < 0.05; **P < 0.01; ***P < 0.001). *n.s.* non significant

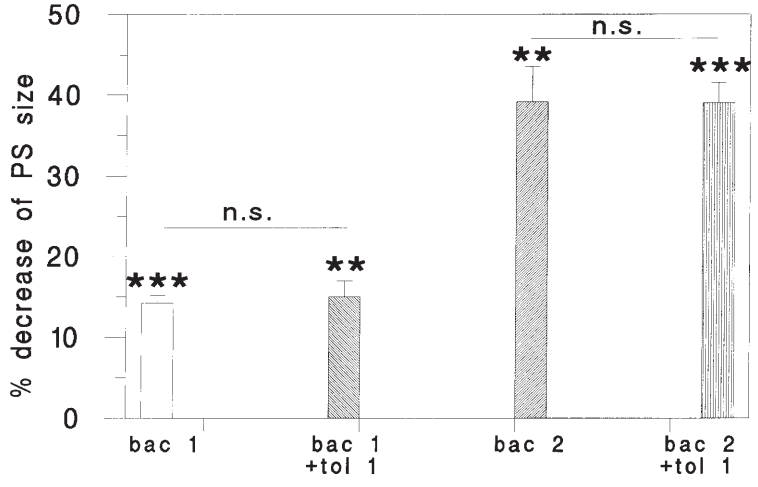

Fig. 4. Histogram showing the effect of baclofen (bac) 1 and 2 μM and tolbutamide (tol) 1 mM on orthodromically evoked CA1 population spikes (PS). Each vertical bar represents the mean ± s.e.m. for n = 4 slices. Student's t test was employed to determine the significance level relative to control potentials or to adenosine alone as indicated (*P < 0.05; **P < 0.01; ***P < 0.001)

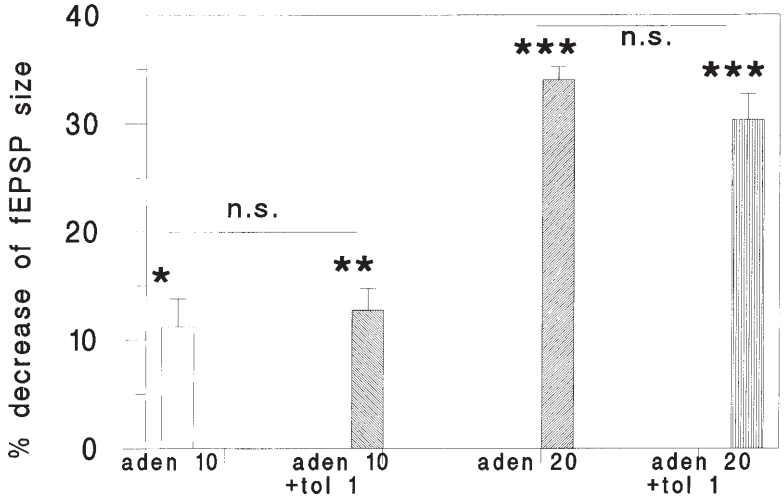

Fig. 5. Histogram showing the effect of adenosine (aden) 10 and 20 μM and tolbutamide (tol) 1 mM on orthodromically evoked CA1 field EPSPs (fEPSP). Each vertical bar represents the mean ± s.e.m. for n = 4. Student's t test was employed to determine the significance level (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). *n.s.* non significant

Baclofen at 2 and 5 μM decreased the size of the field EPSPs by 15.4% ± 2.2 (n = 4, $P < 0.05$) and 28.5% ± 3.1 (n = 4, $P < 0.05$) respectively. Tolbutamide, 1 mM did not affect this presynaptic effect of baclofen at either concentration (n = 4).

Antidromic stimulation

In nominally Ca^{2+} free medium with high magnesium, multiple secondary spikes were obtained in response to antidromic stimulation and stable bursts appeared after about 90 minutes (Fig. 6). Adenosine concentration-dependently decreased the size of the secondary spike with maximal effect at about 20 μM (Fig. 7A). Adenosine at 5 and 10 μM decreased the secondary antidromic spike size by 39.1% ± 5.35 (n = 4, $P < 0.05$) and 53.3% ± 10.33 (n = 4, $P < 0.05$). Tolbutamide 1 mM decreased the effect of adenosine dramatically to 6.3% ± 2.0 (n = 4, $P < 0.05$) and 11.0% ± 0.74 (n = 4, $P < 0.05$) respectively (Fig. 7B). Tolbutamide alone in this series changed the mean size of secondary spikes by 18.88% ± 7.43 (n.s., n = 4). The effect of tolbutamide 1 mM disappeared very quickly on washing the slices, and responses to adenosine were restored to control levels in about 5 minutes.

Baclofen concentration-dependently decreased the amplitude of secondary spikes. Tolbutamide 1 mM had no significant effect on these inhibitory actions of baclofen at 1,2, or 5 μM (Fig. 8), even though tolbutamide alone increased the amplitude of secondary spikes by 25.95% ± 7.67 ($P < 0.05$, n = 4) in this series of experiments.

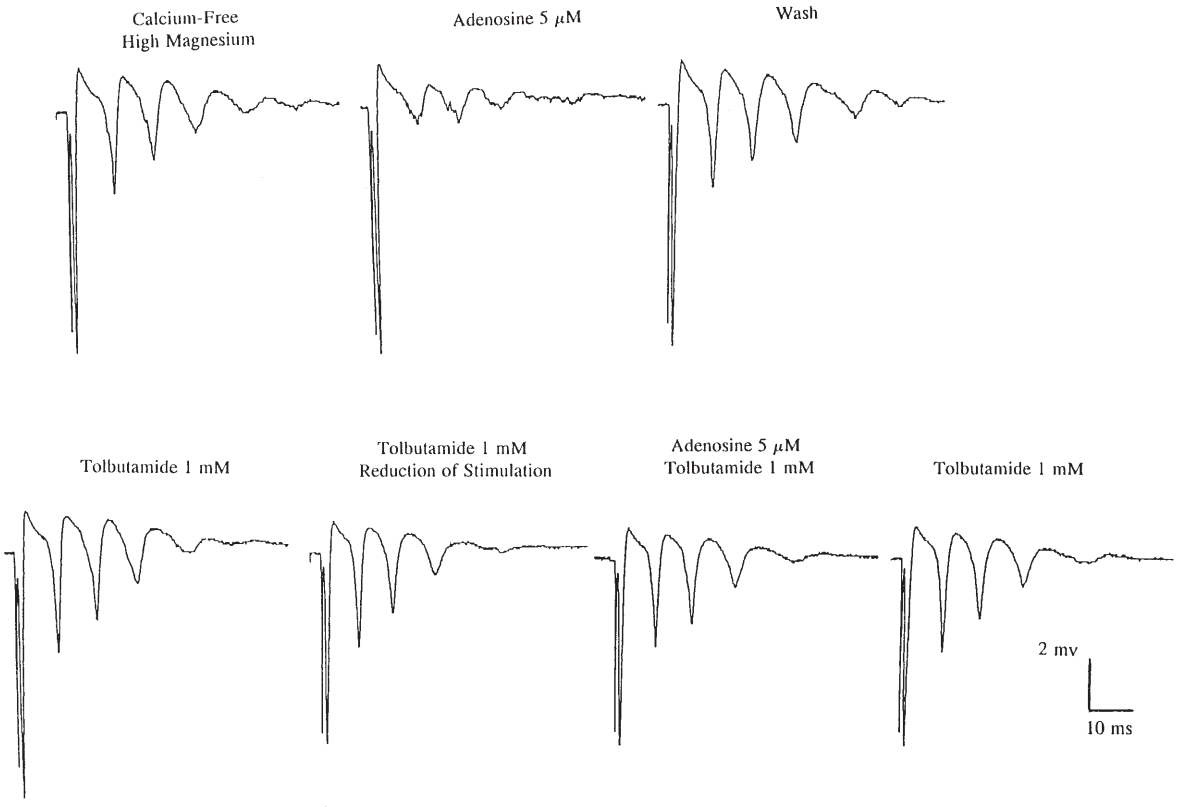

Fig. 6. Sample records of evoked burst activity and the effect of adenosine and tolbutamide on secondary spike size. After the first tolbutamide recording the strength of the stimulus was reduced so as to restore the potential size to the control level seen before any drug addition

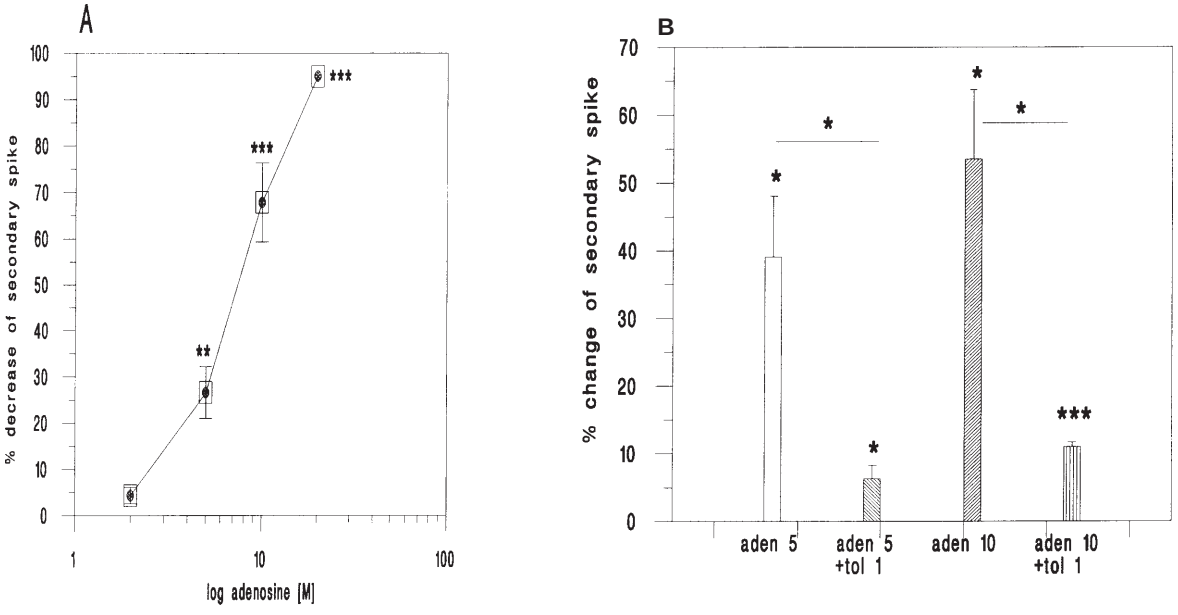

Fig. 7. **A** Cumulative concentration-response curve for the effect of adenosine on the antidromically evoked secondary spike size. Each point represents the mean ± s.e.m. for n = 8. **B** The effect of adenosine (aden) 5 and 10 μM and tolbutamide (tol) 1 mM on antidromically evoked CA1 secondary spikes. Each point represents the mean ± s.e.m. for n = 4. Student's t test was employed to determine the significance level (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$)

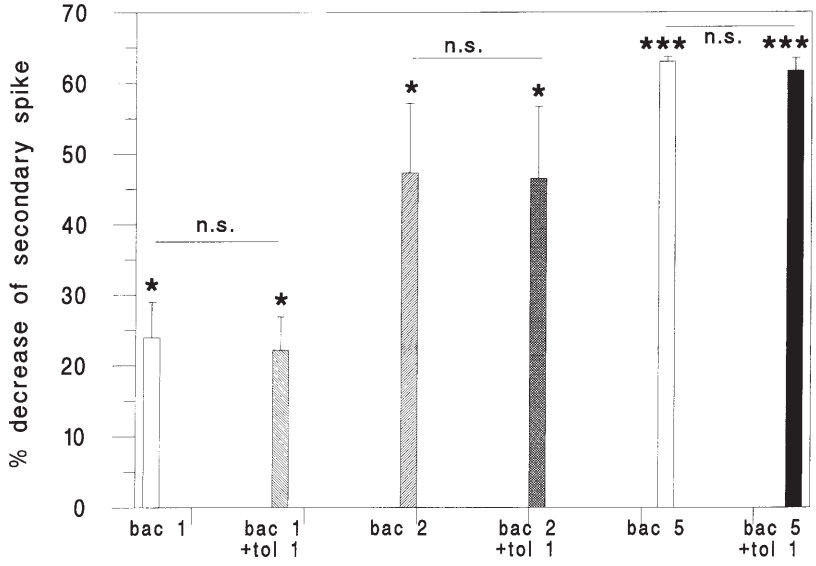

Fig. 8. Histogram showing the effect of baclofen (bac) 1, 2 and 5 μM and tolbutamide (tol) 1 μM on antidromically evoked CA1 secondary spikes. Each vertical bar represents the mean ± s.e.m. for n = 4. Student's t test was employed to determine the significance level (*$P < 0.05$; ***$P < 0.001$). *n.s.* non-significant

Discussion

ATP-sensitive potassium channels link membrane potential variations to the bioenergetic status of the cell. An increase in the intracellular concentration of ATP tends to close this channel and produce a depolarization. In pancreatic cells, where channel function is relatively well understood, depolarization induced by elevated ATP levels subsequent to glucose metabolism opens voltage-gated Ca^{2+} channels to release insulin. Sulphonylurea compounds such as tolbutamide or glibenclamide can block this potassium channel and trigger insulin release (Gopalakrishnan et al., 1993). The existence of sulphonylurea binding sites associated with ATP-sensitive K channels have been shown in the hippocampus and other parts of the CNS (Mourre et al., 1989). Hypoglycaemia or hypoxia can activate K_{ATP} as a neuroprotective mechanism of neuronal cells. For example during anoxia, when cellular levels of ATP decline, these channels are activated and can block glutamate release (Tromba et al., 1992).

The present results suggest K_{ATP} channel involvement in the postsynaptic effect of adenosine and are consistent with a report that an inhibitory postsynaptic potential in spinal nociceptive neurones, apparently mediated by adenosine, was blocked by glibenclamide (Salter et al., 1993). The present result is also consistent with the block of adenosine-induced hyperpolarization by glibenclamide in the hippocampus (Li and Henry, 1992) and a report that in rat ventricular myocytes ATP-sensitive K^+ channels are coupled to adenosine A_1 receptors by G_i (Kirsch et al., 1990). The lack of K_{ATP} involve-

ment in the activity of baclofen is consistent with behavioural evidence that the antinociceptive effect of baclofen is not prevented by gliquidone, a potent K_{ATP} channel blocker (Ocana and Baeyens, 1993). The fact that tolbutamide had no effect on the presynaptic action of adenosine may indicate a totally different mechanism for the pre- and postsynaptic effects. The possible existence of different types of potassium channels activated by adenosine at pre- and postsynaptic sites cannot be excluded.

Indeed, there is evidence that tolbutamide may have pharmacological actions in addition to its blockade of ATP-sensitive channels. In particular, the drug has been shown to block calcium currents as well as a range of potassium currents including $I(_{AHP})$, $I(_{C})$ and $I(_{M})$ (Erdemli and Krnjevic, 1996). It also inhibited the cyclic AMP-dependent chloride current in mucosal cells (Huang and Wong, 1996), though it remains unclear whether this is a direct or indirect action resulting from the blockade of ATP-sensitive channels, and produces open-channel block of the cystic fibrosis chloride channels (Venglarik et al., 1996). Conversely, Satin (1996) has reviewed evidence that tolbutamide can activate a novel form of chloride conductance and inhibit sodium/potassium ATPase activity. As it has been suggested that adenosine may inhibit neurones by actions on ATPase and chloride channels (Mager et al., 1990), these actions of tolbutamide may contribute to the blockade of adenosine in the present report.

Lowering or omitting calcium allows CA1 pyramidal neurones to generate epileptiform bursts after antidromic stimulation (Haas and Jefferys, 1984). In normal ACSF, recurrent, feedforward inhibition and calcium dependent potassium mediated afterhyperpolarization oppose sustained neuronal discharges. Lowering extracellular calcium reduces these processes and removes also the stabilization effect of calcium on the membrane surface charges with the result that multiple action potentials appear. This model of antidromic bursts induced in calcium-free medium with high magnesium is independent of synaptic activity and the inhibitory effects of agents can therefore be ascribed solely to their postsynaptic activity. Lee et al. (1984) have previously shown that adenosine is effective in suppressing this postsynaptic hyperexcitability.

At the postsynaptic sites, the inhibitory actions of both adenosine and baclofen are mainly attributable to hyperpolarization induced by activation of potassium channels. The type of potassium channels activated by these agents, however, is controversial. It is well established that barium can block postsynaptic effects of adenosine (Gerber et al., 1989; Thompson et al., 1992) and baclofen (Gahwiler and Brown, 1985; Misgeld et al., 1989) but since barium has a variety of effects including blocking several different potassium channels, this does not necessarily imply that the same potassium channels are involved. The present results with tolbutamide and antidromically evoked potentials clearly showed that the postsynaptic effect of adenosine and baclofen are different since the inhibitory effect of adenosine on secondary spikes was almost abolished by tolbutamide while this compound had no effect on baclofen sensitivity. This suggests that only the effects of adenosine involve K_{ATP} channels.

When a maximal hyperpolarization response had been evoked with baclofen, Nicoll (1988) found that adenosine was unable to produce any additional response. It was proposed that the receptor mechanisms activated by the two agonists might converge onto a common potassium channel. A similar proposal was made as a result of studies on cells in the cerebral cortex (McCormick and Williamson, 1989). Although this conclusion differs from that drawn from the present work, it may be related to the use of maximal concentrations of agonists by these authors. In particular, maximal concentrations may recruit a population of potassium channels which can be activated by both agents and mask the differential activation of separate channels seen at lower concentrations used in the present work.

In conclusion, the mechanisms of postsynaptic activity of adenosine and baclofen are clearly different and at postsynaptic, but not presynaptic, sites adenosine may activate ATP-sensitive potassium channels. Although the concentrations of adenosine suggested here to activate this channel are higher than the low micromolar concentrations believed to exist under normal physiological or in vitro conditions (Zetterstrom et al., 1982; Feuerstein et al., 1988; Chen et al., 1992; Carswell et al., 1997), the level of adenosine may rise appreciably to or beyond 100 μM as a result of hypoxia or ischaemia (Winn et al., 1979), levels which should then be able to activate these channels.

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