Pharmacology Biochemistry & Behavior, Vol. 55, No. 3, pp. 315–321, 1996

0091-3057/96 $15.00 + .00

ELSEVIER

PII S0091-3057(96)00099-8

Kindled Seizures Do Not Affect Adenosinergic Inhibition of DA or ACh Release in Rat Accumbens or PFC

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Received 17 November 1995; Revised 16 March 1996; Accepted 16 March 1996

ENGELBRECHT, A. H., V. A. RUSSELL, M. MINTZ, M. C. L. LAMM, L. KELLAWAY, L. J. HERBERG AND J. J. F. TALJAARD. *Kindled seizures do not affect adenosinergic inhibition of DA or ACh release in rat accumbens or PFC.* PHARMACOL BIOCHEM BEHAV **55**(3) 315–321, 1996.—Epileptic seizures are thought to terminate largely as a result of the extracellular accumulation of the purinergic neuromodulator, adenosine, released by discharging neurons. However, the postictal surge in extracellular adenosine and its widespread inhibitory effects are limited in time to only a few minutes and cannot directly account for increased resistance to seizures and the complex behavioural and motivational effects that may persist for hours or days after a seizure. The present study examined whether kindled siezures might alter the sensitivity or efficacy of inhibitory presynaptic adenosine receptors, and thereby induce more enduring changes in downstream transmitter systems. Rats were kindled in the amygdala of the dominant cerebral hemisphere, contralateral to the preferred direction of rotation, and their brains were removed either 2 h or 28 days after completion of kindling. Inhibition of electrically stimulated release of dopamine (DA) and acetylcholine (ACh) by the A1 adenosine-receptor agonist, R-phenylisopropyladenosine (R-PIA) was then measured in the prefrontal cortex (PFC) and nucleus accumbens. R-PIA (1.0 μM) inhibited [^{3}H]DA release from PFC and nucleus accumbens tissue, and [^{14}C]ACh release from nucleus accumbens tissue, but release was unaffected by prior kindling, regardless of the intervening interval. These results do not support suggestions that DA or ACh might mediate the effects of seizure-induced changes in purinergic inhibitory tone so as to cause long-term shifts in seizure threshold and postictal behavior.

Acetylcholine Adenosine Amygdala Dopamine Kindling Accumbens Prefrontal cortex

DAILY brain stimulation may lead to the development of kindled epileptic seizures (19), each seizure being followed by a temporary refractory state, during which the threshold for further seizures is raised (1,20,25,36). The biochemical basis of this postictal resistance to seizures is unknown. Postictal resistance to seizures is also associated with long-lasting changes in motivational and affective behavior—as seen after electroconvulsive therapy (14,56), but the nature of the relationship is again quite unknown.

There is strong evidence that individual seizures are initailly halted by extracellular accumulation of adenosine, an inhibitory neuromodulator (47,59) derived from the accelerated degradation of ATP in actively firing neurons (4,11). Extracellular adenosine normally exerts an inhibitory feedback on several different types of neurotransmitter terminal (21,44,54), and is, thus, thought to serve as a wide-ranging protective mechanism against harmful neuronal overactivity (43,49). Neurotransmitter systems known to be affected in this

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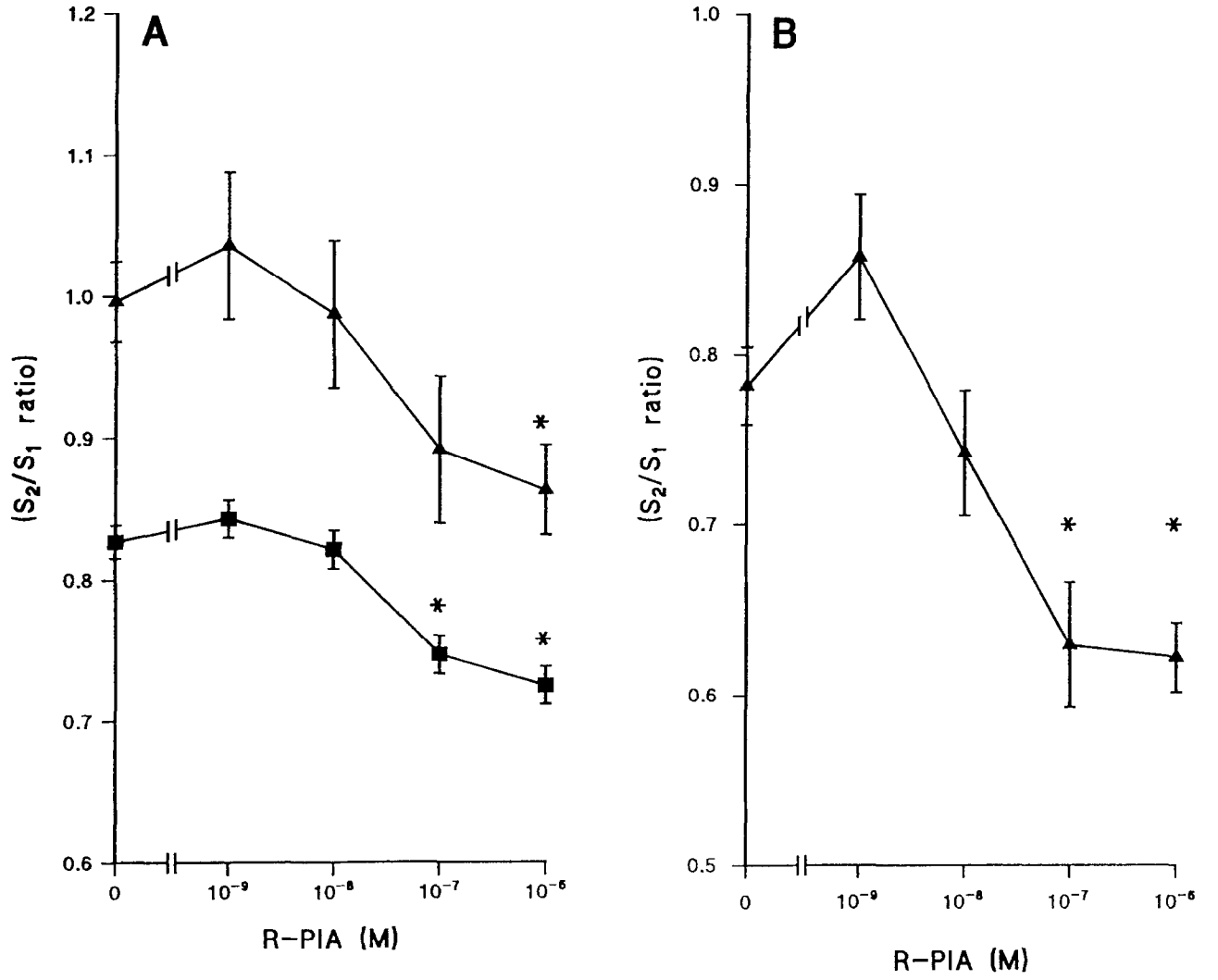

FIG. 1. Concentration-dependent effect of R-PIA on electrically stimulated neurotransmitter release. (A) [^{3}H]DA release from PFC (■) and nucleus accumbens (▲) tissue. (B) [^{14}C]ACh release from rat nucleus accumbens tissue. Results are the mean ± SEM of 3–10 observations. *Significantly different from control (without R-PIA) value (*t*-test, $p = 0.001$ for PFC; $p = 0.005$ for nucleus accumbens [^{3}H]DA; and $p = 0.0024$ and $p = 0.0002$ for 0.1 and 1 μM R-PIA, respectively, for nculeus accumbens [^{14}C]ACh).

way include glutamatergic (8), dopaminergic (15,23,29) and cholinergic, but not striatal GABAergic pathways (6,23). The importance of this feedback is confirmed by the increased seizure duration, sometimes culminating in lethal status epilepticus (2,12,58) produced by small doses of adenosine antagonists, and the converse effects of agonists (5,41).

However, the half-life of extracellular adenosine and its active metabolites is only of the order of a minute or two (32,60), whereas postictal immunity may last for hours or even days (1,25,36,42).

The brevity of the postictal surge in adenosine has led to a search for more prolonged aftereffects (13,24). It has been suggested that surges in adenosine might set up prolonged secondary changes in target pathways, whether by increase in A1 receptor number (10,17) but cf. Wybenga (62), or by more efficient coupling. Target pathways would consequently be more responsive to small perturbations in extracellular adenosine released by prodromal subconvulsive activity, and full-scale seizures would consequently be aborted (52). Adenosine has also been identified as one of "the most potent compounds affecting growth-related processes" (49), acting synergistically with nerve-growth factor (22,46). Nerve-growth factor and related neurotrophins are known, in turn, to facilitate postictal sprouting (3,16,57) and to bring about structural modifications in forebrain and hippocampus after seizure activity (33,39,51). The role of this widespread synaptic reorganization has not been established, but long-term changes in subsequent seizures and their effects seem likely.

The present study examined the short- and long-term effects of kindling-induced surges in adenosine on responsiveness to purinergic stimulation in prefrontal cortex (PFC) and nucleus accumbens. These structures constitute the principal termini of the limbic system and are likely substrates for postictal affective and motivational changes. The study focused on ACh and DA: cholinergic transmission is important for the propagation of established seizures (45), while dopaminergic transmission plays a critical role in motivational processes (61), and may show prolonged changes in response to kindling

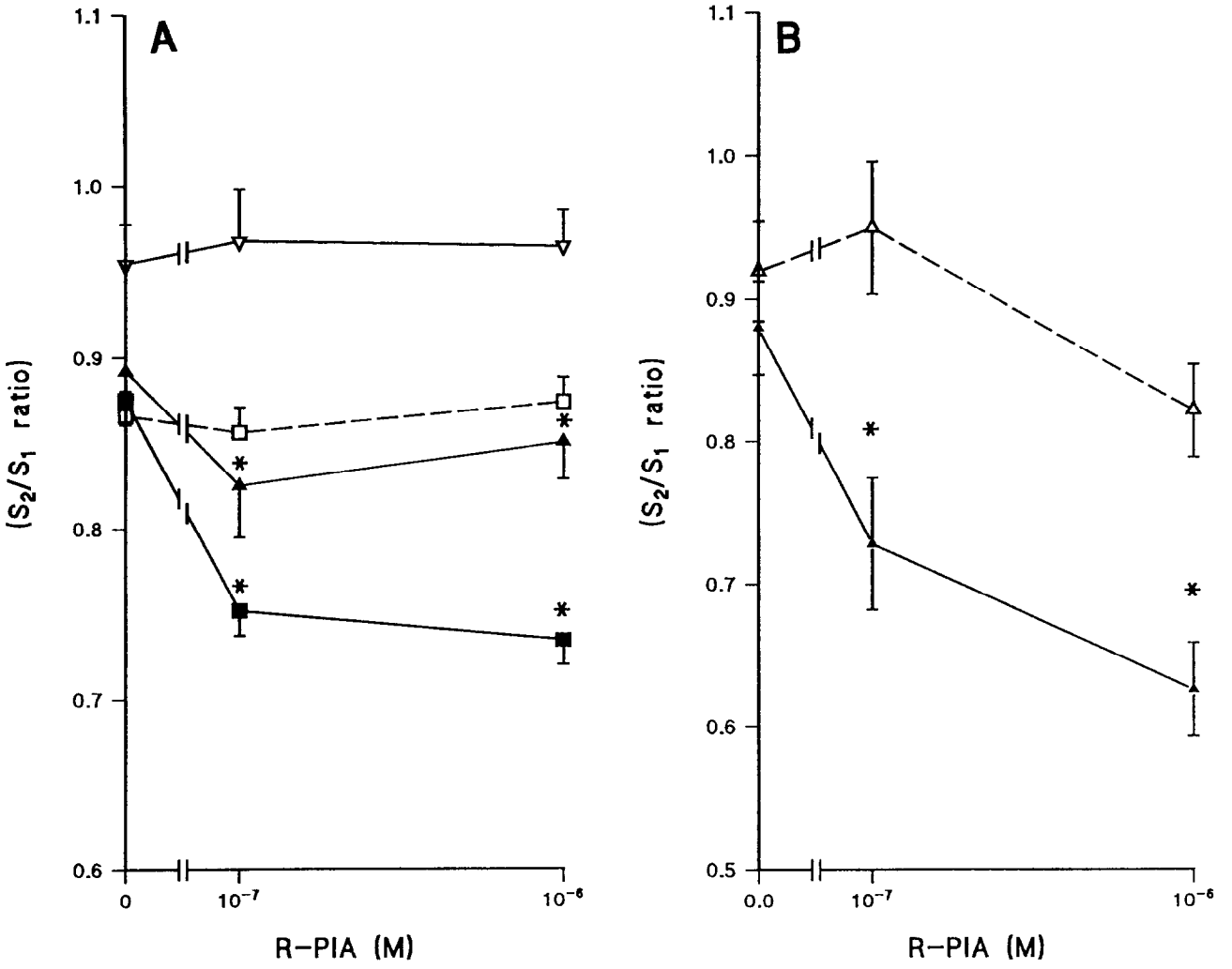

FIG. 2. Antagonism of A1 adenosine receptor-mediated inhibition of the electrically stimulated release of neurotransmitter by 1 μM CPT. (A) [^{3}H]DA release from rat prefrontal cortex (■) and nucleus accumbens (▲) tissue. (B) [^{14}C]ACh release from rat nucleus accumbens tissue. Results are the mean ± SEM of four to eight observations. *Signifcant difference between R-PIA and R-PIA + CPT (*t*-test, $p = 0.0001$ for PFC, $p = 0.0007$ for nucleus accumbens [^{3}H]DA; and $p = 0.0019$ and $p = 0.0002$ for 0.1 and 1 μM R-PIA, respectively, for nucleus accumbens [^{14}C]ACh).

stimulation (9,31,35). Amygdala kindling was carried out exclusively in the dominant hemisphere (defined for present purposes as the hemisphere ipsilateral to the preferred direction of amphetamine-induced rotation) so as to minimize confounding effects of interhemispheric DA asymmetry (18,48). The effect of the selective and metabolically stable A1-receptor agonist, R-PIA on electrically stimulated release of [^{3}H]DA and [^{14}C]ACh was then determined in prefrontal and accumbens tissue from both ipsi- and contralateral hemispheres at intervals of 2 h or 28 days after kindling or sham kindling.

METHOD

Subjects

Male Long–Evans rats (260–300 g) were housed in single cages under standard laboratory conditions with a 12 L:12 D cycle. Interhemispheric DA imbalance was inferred from the number of right and left rotations in a rotometer during 60 min after administration of *d*-amphetamine [1.5 mg/kg IP; (26,28)]. Only rats with clear behavioral asymmetry were included in the study. Five days after assessment of rotational preference, rats were anaesthetized with Equithesin (4.5–5.0 ml/kg IP). Bipolar spring-steel electrodes (0.3 mm in diameter, 1.0 mm apart, and electrically insulated with Epoxylite resin except for the 0.4-mm tips) were stereotaxically implanted in the basolateral nucleus of the amygdala in the dominant cerebral hemisphere, contralateral to the preferred direction of rotation. Target coordinates were 5.6–6.6 mm anterior to the plane of the interaural line, 4.6 mm lateral to the midline, and 8.8 mm ventral to bregma (37). Biochemical measurements are specified as ipsi- or contralateral in relation to the side of the electrodes.

Kindling

Kindling commenced 5 days after surgery and consisted of one or two daily stimulations (1.5-s trains of 100-Hz square bipolar pulses, each of 0.4 mA and 0.1 ms duration), with a

TABLE 1

EFFECT OF KINDLING ON R-PIA–MEDIATED INHIBITION OF [^{3}H]DA RELEASE FROM RAT PREFRONTAL CORTEX TISSUE

	Electrically Stimulated Release of [^{3}H]DA (S_2/S_1)					
	Sham-Kindled Rats			Kindled Rats		
Time, Side	−R-PIA	+R-PIA	% Inhb	−R-PIA	+R-PIA	% Inhb
Short term						
Ipsi	0.869 ± 0.0163	0.763 ± 0.0126*	12	0.881 ± 0.0168	0.790 ± 0.0134*	10
Contra	0.875 ± 0.0101	0.770 ± 0.0168*	12	0.854 ± 0.0219	0.768 ± 0.0195*	10
Long term						
Ipsi	0.905 ± 0.0192	0.798 ± 0.0142*	12	0.878 ± 0.0173	0.763 ± 0.0199*	13
Contra	0.902 ± 0.0280	0.760 ± 0.0165*	16	0.865 ± 0.0148	0.766 ± 0.0167*	12

Results are the mean ± SEM of duplicate determinations on 14–17 rats. Rats were decapitated 2 h (short term) or 28 days (long term) after the final kindled seizure. Prefrontal cortex tissue was stimulated electrically in the presence or absence of R-PIA. Ipsi and contra refer to the hemisphere ipsilateral and contralateral to the kindled amygdala.

*Significantly different from −R-PIA value, $p < 0.001$ (paired t-test).

minimum intertrial interval of 7 h. Seizure progression was rated on Racine's six-point scale (38). Rats were kindled until they had displayed five stage 5 seizures, achieved in 80% of the kindled rats after approximately 25–29 stimulations. Sham-kindled rats were treated identically except that they did not receive electrical stimulation.

Release Studies

The concomitant release of DA and ACh was measured using an in vitro superfusion system (34,40). Electrical stimulation was applied across the superfusion chamber to induce depolarisation, and the electrically stimulated release of [^{3}H]DA and [^{14}C]ACh was measured. The concentration of R-PIA required to induce maximal inhibition of stimulated release of [^{3}H]DA and [^{14}C]ACh was determined in preliminary studies on unoperated rats. The selective adenosine A1 receptor antagonist, cyclopentyltheophylline [CPT; (7)] was used to antagonise the effect of R-PIA.

After decapitation, the brains of unoperated or kindled and sham-kindled rats were rapidly removed, cooled on ice and sliced coronally with a McIlwain tissue chopper. Prefrontal cortices were dissected from the first two or three slices and consisted of the tissue anterior to the genu of the corpus callosum. The accumbens nuclei were distinguished from surrounding tissue and dissected from the next three more caudal brain sections, 11.2–9.7 mm anterior to the interaural line (37). Dissected sections were kept on ice. Tissue slices were cut with a McIlwain tissue chopper (0.3 × 0.3 mm) and the chopped tissue suspended in aerated Krebs buffer adapted from Kamal et al. (30) [118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2 \cdot 6H_2O$, 1.0 mM NaH_2PO_4, 1.3 mM $CaCl_2$, 25 mM $NaHCO_3$, 11 mM glucose, and 0.04 mM ethylenediamine tetraacetic acid (EDTA), adjusted to pH 7.3 by aeration with 95% O_2/5% CO_2] at a concentration of 1:50 (original tissue w:v). This buffer was kept under an atmosphere of 95% O_2/5% CO_2. During incubation, the Krebs buffer contained an antioxidant, ascorbate (5.7 μM), a MAO inhibitor, pargyline (10 μM) to block DA metabolism and increase tissue levels of [^{3}H]DA (55), the NA uptake inhibitor, desipramine [1.0 μM; (53)], and a 5-HT uptake inhibitor, citalopram [1.0 μM; (27)]. After a 10-min equilibration period, [^{3}H]DA and [^{14}C]choline were added to the tissue preparation at 37°C to give a final concentration of 0.06–0.08 μM 3,4-[7-^{3}H]DA (24–32 Ci/mmol) and 3.5–3.7 μM [methyl-14C]choline chloride (53–58 mCi/mmol). After an additional 15-min incubation period, the tissue preparations were cooled on ice and washed three times with ice cold incubation buffer.

Portions of the incubated tissue were transferred to either 8 or 16 superfusion chambers and subjected to continuous superfusion (0.23 ml/min at 37°C) as previously described (34). Buffer flowed through the chambers, which were embedded in a perspex waterbath maintained at 37°C, via stainless steel needles that were connected by plastic tubing to a multichannel pump and buffer reservoirs on the one side, and a fraction collector on the other. The stainless steel provided the contacts for application of electrical current across the tissue. Five-minute fractions of eluate were collected after a 90-min wash period with drug-free Krebs buffer. Twenty minutes before fraction collection, 1.0 μM amineptine was added to the superfusion buffer of the accumbens tissue for the purpose of enhancing the detection of [^{3}H]DA release by inhibiting its reuptake. This was not necessary for PFC tissue because DA release was much higher there than from nucleus accumbens tissue. After collection of the first two fractions to establish baseline neurotransmitter release, an electrical stimulation train (S_1) consisting of bipolar square wave pulses (2 ms duration, 5 Hz frequency, and 16 mA amplitude) was delivered for 2 min. Drugs, R-PIA (0.1–1.0 μM) or CPT (1.0 μM) were added to the test columns 12 min before the second stimulation period (S_2), and remained present for the rest of the experiment. The second electrical stimulation period was initiated 40 min after the first, and five more fractions were collected to reestablish baseline neurotransmitter release. The contents of each column were expelled and the radioactivity extracted with 2 ml 0.1 M HCl overnight. Radioactivity in the superfusate fractions, as well as residual radioactivity in the columns were determined in a Packard 2200 CA TRI-CARB liquid scintillation analyser.

Calculation

The fractional release of [^{3}H]DA and [^{14}C]ACh was calculated by dividing the amount of radioactivity released during each collection period by the sum of the radioactivity in that and subsequent collection periods plus the radioactivity remaining in the tissue. The area of the peak of neurotransmitter release above the spontaneous outflow was determined from

TABLE 2

EFFECT OF KINDLING ON R-PIA–MEDIATED INHIBITION OF [^{3}H]DA RELEASE FROM RAT NUCLEUS ACCUMBENS TISSUE

	Electrically Stimulated Release of [^{3}H]DA (S_2/S_1)					
	Sham-Kindled Rats			Kindled Rats		
Time, Side	−R-PIA	+R-PIA	% Inhb	−R-PIA	+R-PIA	% Inhb
Short term						
Ipsi	0.963 ± 0.0090	0.916 ± 0.0288*	5	0.957 ± 0.0294	0.866 ± 0.0162‡	10
Contra	0.986 ± 0.0305	0.902 ± 0.0203*	9	0.931 ± 0.0111	0.874 ± 0.0196*	6
Long term						
Ipsi	0.991 ± 0.0133	0.889 ± 0.0235†	10	0.969 ± 0.0275	0.902 ± 0.0368*	7
Contra	0.987 ± 0.0380	0.890 ± 0.0262‡	10	0.988 ± 0.0367	0.904 ± 0.0227*	8

Results are the mean ± SEM of single determinations on 12–18 rats. Rats were decapitated 2 h (short term) or 28 days (long term) after the final kindled seizure. Nucleus accumbens tissue was stimulated electrically in the presence or absence of R-PIA. Ipsi and contra refer to the hemisphere ipsilateral and contralateral to the kindled amygdala.

*Significantly different from −R-PIA value, $p < 0.05$; †$p < 0.001$; ‡$p < 0.01$ (paired t-test).

the fractional release data of each individual column. S_1 represents the electrically stimulated release of neurotransmitter before drug addition, and S_2 represents the release in the presence of the drug. The S_2/S_1 ratio was used to determine the effect of the drug on neurotransmitter release. The S_2/S_1 ratios of kindled and control rat groups were compared to determine the effect of kindling on adenosine-mediated inhibition of the electrically stimulated fractional release of [^{3}H]DA and [^{14}C]ACh.

Statistical Analysis. Analysis of variance (ANOVA) with between-rat factors of treatment (control vs. kindled) and time (short vs. long term), and within-rat factors of side (ipsi- vs. contralateral) and drug (superfusion with or without R-PIA) was performed on the S_2/S_1 data for each neurotransmitter (DA and ACh) and for each brain area (PFC and nucleus accumbens). The effect of kindling on ACh release could not be determined in the PFC, because [^{14}C]ACh levels were too low to permit reliable interpretation.

RESULTS

Transmitter Release in Unoperated Rats

The specific adenosine A1 receptor agonist, R-PIA, inhibited the electrically stimulated release of [^{3}H]DA from PFC and nucleus accumbens tissue in a concentration-dependent manner (Fig. 1A). This effect of R-PIA was significant both in PFC, $F(4, 27) = 15.61, p = 0.0001$, and in nucleus accumbens, $F(4, 22) = 3.65$, $p = 0.020$. Maximal inhibition of [^{3}H]DA release was observed at a concentration of 1.0 μM R-PIA (12 and 13% inhibition of [^{3}H]DA release from PFC and nucleus accumbens tissue, respectively).

R-PIA also caused a concentration-dependent decrease in the electrically stimulated release of [^{14}C]ACh from nucleus accumbens tissue, $F(4, 18) = 10.45$, $p = 0.0001$; Fig. 1B. The inhibitory effect of R-PIA on [^{14}C]ACh release (maximum 20% inhibition at 1.0 μM R-PIA) was much greater than the effect on [^{3}H]DA release.

The inhibitory effect of R-PIA (0.1 μM and 1.0 μM) on [^{3}H]DA release was significantly antagonised by the selective adenosine A1 receptor antagonist, CPT (1.0 μM) in PFC, $F(5, 30) = 19.91$, $p = 0.0001$ (Fig. 2A), and in nucleus accumbens tissue, $F(5, 33) = 6.00$, $p = 0.0005$ (Fig. 2A). CPT (1 μM) also antagonised the effect of R-PIA (0.1 μM and 1.0 μM) on [^{14}C]ACh release from nucleus accumbens tissue, $F(5, 33) = 11.68$, $p = 0.0001$ (Fig. 2B).

Transmitter Release in Kindled Rats

The S_2/S_1 ratio was used to evaluate the effect of kindling on the R-PIA–mediated inhibition of the electrically stimulated release of neurotransmitters from PFC ([^{3}H]DA) and nucleus accumbens ([^{3}H]DA and [14C]ACh) tissue.

R-PIA significantly inhibited [^{3}H]DA release from PFC tissue of both kindled and sham-kindled rats, $F(1, 60) = 218$, $p = 0.0001$, but there was no significant difference between kindled and control rats with respect to the magnitude of the effect of R-PIA (Table 1). There were also no short- vs. long-term, or ipsi- vs. contralateral differences in the R-PIA effect. The differences between the effects of R-PIA on [^{3}H]DA release in short-term kindled rat tissue (10% inhibition), long-term kindled rat tissue (13 and 12% inhibition), and control tissue (12% inhibition) also fell short of significance, $F(1, 57) = 1.08$, $p = 0.304$ (Table 1).

R-PIA significantly inhibited [^{3}H]DA release (Table 2) from both kindled and sham-kindled accumbens tissue, $F(1, 66) = 53$, $p = 0.0001$. The inhibitory effect of R-PIA on [^{3}H]DA release in the nucleus accumbens was less than that observed for the PFC and varied from 5 to 10%. There was no significant effect of treatment (control vs. kindled), time (short vs. long term), or side (ipsi- vs. contralateral) on [^{3}H]DA release from nucleus accumbens tissue.

The inhibitory effect of R-PIA on [^{14}C]ACh release (Table 3) from kindled and control rat nucleus accumbens was significant, $F(1, 66) = 242$, $p = 0.0001$, but effects of treatment, time, and side were not significant. The effect of R-PIA ranged from 20 to 27%, and was greater than the effect on [^{3}H]DA release observed in either the accumbens or PFC.

DISCUSSION

R-PIA (1.0 μM), caused a maximum of 12–13% inhibition of the electrically stimulated release of [^{3}H]DA from PFC and nucleus accumbens, and 20% inhibition of [^{14}C]ACh release from nucleus accumbens tissue. This result is consistent with the binding studies of Brown et al. (6) who found maximal displacement of [^{125}I]-hydroxy PIA at 1.0 μM R-PIA. The

TABLE 3

EFFECT OF KINDLING ON R-PIA–MEDIATED INHIBITION OF [^{14}C]ACh RELEASE FROM RAT NUCLEUS ACCUMBENS TISSUE

	Electrically Stimulated Release of [^{14}C]ACh (S_2/S_1)					
	Sham-Kindled Rats			Kindled Rats		
Time, Side	−R-PIA	+R-PIA	% Inhb	−R-PIA	+R-PIA	% Inhb
Short term						
Ipsi	0.902 ± 0.0202	0.673 ± 0.0224*	25	0.930 ± 0.0271	0.710 ± 0.0461*	24
Contra	0.863 ± 0.0274	0.664 ± 0.0367*	23	0.930 ± 0.0443	0.698 ± 0.0316†	25
Long term						
Ipsi	0.889 ± 0.0245	0.667 ± 0.0341*	25	0.882 ± 0.0309	0.706 ± 0.0379*	20
Contra	0.926 ± 0.0195	0.681 ± 0.0218*	27	0.909 ± 0.0191	0.694 ± 0.0348*	24

Results are the mean ± SEM of single determinations on 13–18 rats. Rats were decapitated 2 h (short term) or 28 days (long term) after the final kindled seizure. Nucleus accumbens tissue was stimulated electrically in the presence or absence of R-PIA. Ipsi and contra refer to the hemisphere ipsilateral and contralateral to the kindled amygdala.

*Significantly different from −R-PIA value, $p < 0.001$; †$p < 0.01$ (paired t-test).

specificity of the R-PIA effect was confirmed by antagonism by the selective adenosine A1 receptor antagonist, CPT.

In order to determine whether kindling altered the effect of R-PIA on the electrically stimulated release of DA from PFC tissue, the S_2/S_1 ratios of kindled and control rats were compared. Statistical analysis revealed that there was no kindling effect. The inhibitory effect of R-PIA was similar in short- and long-term groups and there were no ipsi- vs. contralateral differences.

Similarly, kindling did not alter the effect of R-PIA on [^{3}H]DA and [^{14}C]ACh release from nucleus accumbens tissue. The inhibitory effect of R-PIA on [^{3}H]DA release was less than that observed in the PFC. This might have been due to higher endogenous concentrations of accumbens adenosine, which could interfere with the measurement of A1 receptor function.

The present results fail to reveal any enduring change in A1 receptor function as a consequence of kindled seizures. No differences were observed in the effects of R-PIA on DA or ACh release from PFC or accumbens tissue of long-term kindled and control rats. It, therefore, seems that the kindling process does not involve a readjustment of purinergic control of DA or ACh release in the PFC or nucleus accumbens. Stone and Lloyd (50) have similarly found no difference in the number or affinity of adenosine receptors in the brains of seizure-prone and seizure-free mice.

Our findings do not directly exclude possible effects on the release of glutamate or other agents affecting susceptibility to seizures, but our results accord with the lack of direct evidence for abnormalities in adenosine neurochemistry in animal models of epilepsy or in epileptic patients (11).

ACKNOWLEDGEMENTS

We are grateful to the S. A. Medical Research Council, the Cape Provincial Administration, and the UK Brain Research Trust for support. We thank Prof. S. Maritz for performing the statistical analysis. Some of this work was submitted by A. H. Engelbrecht in partial fulfilment of his Ph.D. degree.

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