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Short communication

RAPHE NEURONS: FIRING RATE CORRELATES WITH SIZE OF DRUG RESPONSE

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Significant negative correlations were obtained between the spontaneous discharge rate during waking and the neural response to systemic injections of either 5-MeODMT or LSD for serotonergic neurons in the dorsal raphe nucleus, nucleus centralis superior, and nucleus raphe pallidus of unanesthetized and unrestrained cats These data are discussed in terms of an hypothesis which accounts for both the rate of spontaneous activity of serotonergic neurons and the magnitude of their response to serotonin agonist drugs in terms of autoreceptor density on individual neurons

Raphe nuclei Autoreceptors Serotonin Freely moving cats Single unit activity

1. Introduction

In a previous report (Heym et al., 1982a), we noted that the unit discharge rate of serotonergic neurons in the medullary nucleus raphe pallidus (NRP) of freely moving cats was relatively insensitive to systemic injections of LSD or 5-methoxy-N,N-dimethyltryptamine (5-MeODMT). By contrast, the activity of serotonergic neurons in the mesencephalic nucleus raphe dorsalis (DRN) was strongly depressed by systemic administration of the same doses of these two compounds. We had also found that neurons in NRP generally tended to manifest a higher spontaneous discharge rate than neurons in DRN (Trulson and Jacobs, 1979; Heym et al., 1982b). Since LSD and 5-MeODMT are known to act upon the cell bodies of serotonergic neurons, presumably at autoreceptors (De Montigny and Aghajanian, 1977), we speculated that the differential drug sensitivity of NRP and DRN neurons might be attributable to a difference in autoreceptor density (Heym et al., 1982a). Furthermore, since autoreceptors are thought to play an important role in the regulation of serotonergic neuronal activity (Aghajanian, 1981), we hypothesized that the higher spontaneous discharge rate of NRP neurons, as compared to DRN neurons, might also be attributable to this presumed difference in autoreceptor density (Heym et al., 1982a).

In the present study we continue this line of investigation by correlating the magnitude of neuronal response to LSD or 5-MeODMT, *within* a particular serotonergic cell group, with the spontaneous neuronal discharge rate.

2. Materials and methods

Adult female cats (2.4-3 2 kg) were anesthetized with pentobarbital (35 mg/kg i.p.) and prepared for chronic single unit recording using a procedure that has been described in detail previously (Trulson and Jacobs, 1979). Briefly, two microelectrode bundles, each consisting of 6 flexible insulated nichrome wires (3 each of 32 and 64 μm diameter were stereotaxically implanted above the NRP (at an angle of 15° behind the vertical), nucleus centralis superior (NCS) (at an angle of 40° be-

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hind the vertical), or the DRN (at an angle of 45° behind the vertical). Stereotaxic coordinates for the initial placement of the anterior bundles were P 9.5, L 0 0, H −7.5 for the NRP; P 2.7, L 0 0, H −1.3 for the NCS; and P 1.5, L 0.0, H +1.0 for the DRN. The microelectrode bundles were attached to a mechanical microdrive in order to advance them gradually through the brain

Serotonergic neurons of the NRP, NCS, and DRN were identified initially by their characteristic slow, regular discharge and pronounced decrease in firing rate during REM sleep (Heym et al, 1982b; Rasmussen et al, 1982; Trulson and Jacobs, 1979). On occasion, the activity of two serotonergic neurons was recorded concurrently, however, most of the data reported herre are derived from recordings of one cell at a time. After obtaining 10-15 min of baseline activity during waking, animals were administered either 5-MeODMT (50 or 250 μg/kg i m), or d-LSD (50 μg/kg i.p), and, recordings then were continued for up to 2 h post-drug When the same cat was utilized more than once in an experiment, a minimum of seven days intervened between successive injections of LSD since this compound is known to produce long-lasting tolerance By contrast, 5-MeODMT was sometimes injected on successive days since there is little evidence for the development of tolerance to this compound. In general, when a given cat was administered a drug more than once, there was no evidence of a trend toward either an enhanced or diminished neuronal response over time.

The baseline firing rate was calculated for each unit by taking the mean of six consecutive 10 s time samples during pre-drug waking. Post-drug firing rates were calculated for each unit in a similar manner using time samples at 5, 10, 15, 30, 45 and 60 min post-drug. The maximal percent decrease from baseline (typically 10-30 min post-drug for 5-MeODMT and 30-60 min post-drug for LSD) in unit activity for each neuron was then obtained and used in conjunction with that same neuron's baseline firing rate to calculate a correlation coefficient (Pearson's product-moment coefficient). This was done separately for neurons in each of the three groups of serotonergic neurons and in response to each drug administered. At the end of the experiments recording sites were located histologically utilizing a technique which has been described previously (Trulson and Jacobs, 1979).

3. Results

A total of 75 presumed serotonergic cells were studied in 21 different animals in this series of experiments. They were initially identified as serotonergic on-line on the basis of their slow and regular unit discharge pattern Most of these cells were also studied across the sleep-wake cycle and showed a complete, or near complete, suppression of activity during REM sleep, a finding which is characteristic of serotonergic neurons in general (Jacobs et al., 1983) Finally, the localization of all recording sites were found to be within the areas of the cat brainstem where serotonergic neurons are known to be densely localized (Jacobs et al.,

TABLE 1

Correlation analysis between spontaneous unit discharge rate during waking and magnitude of suppression (percent reduction from baseline activity) of unit discharge rate for serotonergic neurons in three brain areas and in response to two different drugs

Serotonergic cellgroup	n	Drug (dose and route)	Baseline rate (spikes/s)	Drug response ($\bar{X}$ percent ↓)	Slope	Intercept	Correlation coefficient (r) [a]	Significance level P
DRN	29	LSD (50 μg/kg i p)	2 84	55 3	−14 3	96 0	−0 52	< 0 01
DRN	10	5-MeODMT (50 μg/kg i m)	1 96	76 6	−16 9	109 7	−0 64	< 0 05
NCS	11	5-MeODMT (50 μg/kg i m)	2 19	45 2	−30 8	112 8	−0 84	< 0 01
NRP	18	5-MeODMT (250 μg/kg i m)	4 27	81 3	−5 6	105 3	−0 53	< 0 05
NRP	7	5-MeODMT (50 μg/kg i m)	3 25	15 7	−6 8	44 8	−0 98	< 0 001

[a] Pearson product, moment correlation coefficient

submitted for publication; Wiklund et al., 1981). These areas corresponded to the DRN, NCS and NRP

As shown in table 1, a total of 39 cells were studied in the DRN, 11 cells were studied in NCS, and 25 cells were studied in NRP Consistent with our previous reports, serotonergic neurons in the DRN and NCS discharged at similar rates during quiet waking ($\bar{X} = 2.6$ and 2 2 spikes/s respectively), while NRP neurons discharged at a substantially higher spontaneous rate ($\bar{X} = 4\,0$ spikes/s). Significant negative correlations were obtained between the spontaneous discharge rates of serotonergic neurons within a particular raphe nucleus and their degree of suppression (percent below baseline) following drug administration (see table 1 for details).

4. Discussion

These results indicate that a significant relationship exists between the spontaneous discharge rate of serotonergic neurons and the degree to which they are influenced by the serotonin agonist drugs, LSD and 5-MeODMT. This appears to be a general characteristic of serotonergic neurons since we observed a similar effect in three different groups of serotonergic cells distributed across the cat brainstem. Furthermore, the effect is not specific to a particular drug since we have observed similar effects with two different serotonin agonist compounds.

The response of serotonergic neurons to serotonin agonist drugs such as LSD and 5-MeODMT appears to be mediated by an action at autoreceptors localized on the cell bodies of these neurons Autoreceptors also appear to regulate the activity of these neurons, presumably by means of interconnections between serotonergic neurons and/or axon collateral feedback (Aghajanian, 1981; Jacobs et al., 1983) Therefore, it seems reasonable to hypothesize, in light of our present correlational analyses, that these two characteristics of individual serotonergic neurons (rate and drug sensitivity) are dependent, at least in part, upon a common variable, namely, the density of autoreceptors. In this light, our previous data regarding differences between nuclei (Heym et al., 1982a), may be reinterpreted as differences in the relative distribution of particular types of serotonergic neurons within these nuclei, rather than differences in the nuclei per se. Thus, if one considers all serotonergic cells on a continuum of autoreceptor density, then the NRP may contain a predominance of cells with low autoreceptor density (fast firing and drug unresponsive) while the DRN and NCS may contain a predominance of cells with high autoreceptor density (slow firing and drug responsive) This hypothesis is supported by our data since a minority of the cells in the NRP were slow firing and drug responsive and a minority of the cells in the DRN and NCS were fast firing and drug unresponsive We are currently attempting to examine this issue more directly by autoradiographic analysis of the number of [^{3}H]LSD binding sites over immunocytochemically identified serotonergic neurons in different brain areas

Other interpretations for these results are also possible. for example, serotonergic neurons may fire faster because of a stronger excitatory afferent input. If these faster firing cells are more tonically depolarized they may simply be less responsive to the hyperpolarizing effects of drugs such as LSD (Aghajanian and VanderMaelen, 1982) It should also be pointed out that some other variable(s) is also exerting an influence, since the slopes of the regression lines vary across serotonergic cell groups.

Finally, this general line of thinking regarding autoreceptor control of both spontaneous activity and drug response may generalize beyond serotonergic neurons Shepard and German (1982) recently reported that slower firing dopaminergic cells in the pars compacta of the substantia nigra of chloral hydrate anesthetized rats were also more responsive to the depressant effects of systemically administered apomorphine Since apomorphine is known to exert its action upon autoreceptors localized on dopaminergic cell bodies, these authors also proposed that a relationship may exist between dopamine cell discharge rate and drug sensitivity It will be interesting, in future studies, to see whether such a relationship also holds for other central neurons whose activity is known to be

regulated, at least in part, by autoreceptors, such as brain noradrenergic neurons.

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