Effects of TRH and an Analog, DN-1417 on the Activities of Single Neurons in the Nucleus Accumbens, Cerebral Cortex and Caudate-putamen of Rats

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Summary: The actions of TRH and its analog, γ -butyrolactone- γ -carbonyl-histidyl prolinamide citrate (DN-1417) on the unit activities of the cerebral cortex, caudate-putamen and nucleus accumbens were examined using a microelectrophoretic technique in anesthetized rats. Over 80 % of the neurons examined in the nucleus accumbens responded to TRH and DN-1417. The effects were mainly inhibitory, but excitatory effects (12-17 %) were also detected. In the cerebral cortex and caudate-putamen, only one-third of the neurons were depressed by TRH and DN-1417. DN-1417 exerted an effect similar to TRH on almost all neurons. Dopamine affected almost all neurons. Its main effect was inhibition, but excitation was also observed in some neurons of the nucleus accumbens. Methamphetamine mimicked dopamine in the three regions. However, it was observed that TRH and DN-1417 mimicked dopamine only in the nucleus accumbens neurons. Furthermore, both the inhibitory and excitatory actions of TRH, DN-1417 or dopamine were attenuated by the dopamine receptor antagonist, haloperidol, which was administered systemically. These results suggest that: (1) TRH and DN-1417 have similar actions on the neurons; (2) TRH and DN-1417 act more selectively than dopamine and methamphetamine on the nucleus accumbens neurons, and they may act indirectly on dopaminergic neurons of the nucleus accumbens through an action on pre-synaptic sites; (3) Endogenous TRH may play a physiological role as a neuro-modulator of dopaminergic transmission in the nucleus accumbens.

Key words: TRH — DN-1417 — dopamine — unit recording — microelectrophoresis — nucleus accumbens — rat

Introduction

Thyrotropin-releasing hormone (TRH), a hypothalamic substance which regulates pituitary-thyroid function, is widely distributed in the brain (Hökfelt et al. 1975; Winokur and Utiger, 1975). It has been shown that TRH produces many central nervous effects, such as antagonism to central depressants (Breese et al. 1975), potentiation of the actions of L-DOPA

(Plotnikoff et al. 1972) and a motor stimulatory action (Goujet et al. 1975). Also, nerve terminals containing TRH (Hökfelt et al. 1975), high affinity TRH-binding sites (Burt and Snyder, 1975) and TRH degradation enzymes (Griffiths et al. 1976) have been found within the brain. It has been proposed that TRH may act as a neurotransmitter or neuromodulator within the central nervous system (Emson, 1979; Morley, 1979; Snyder, 1980).

Miyamoto and Nagawa (1977) reported that the nucleus accumbens is an important site for the locomotor stimulatory action of TRH because bilateral injection of TRH into the nucleus accumbens, regarded as the terminal part of the mesolimbic dopaminergic system, exerted a more prominent stimulatory action than injection into other brain regions. Also, the TRH effect was markedly attenuated by pretreatment with haloperidol, a dopamine receptor antagonist. There is also neurochemical evidence that TRH increases [^3H]-dopamine release from superfused slice preparations of the rat nucleus accumbens and striatum (Kerwin and Pycock, 1979; Narumi et al. 1979).

The nucleus accumbens, mesolimbic dopaminergic system terminus, receives efferent inputs from the ventral tegmentum A10 (Anden et al. 1966) and limbic structures, including the amygdala, hippocampus and cingulate gyrus, related to emotional activity. It projects to the globus pallidus and substantia nigra thereby controlling the motor performance (Conrad and Pfaff, 1976; DeFrance and Yoshihara, 1975; Dray and Oakley, 1977; Ito et al. 1974; Nauta et al. 1978; Takaori et al. 1981). The inputs from the amygdala and A10 converge on the nucleus accumbens (Mogenson et al. 1980; Yim and Mogenson, 1982). Mogenson et al. (1980) proposed that the nucleus accumbens acts as a functional interface between emotional inputs from the limbic system and motor outputs to the nigrostriatal dopaminergic system.

In the present investigation, the effect of TRH on the single neuron activities of the nucleus accumbens, cerebral cortex and caudate-putamen were examined with microelectrophoretic methods. The effect of a TRH analog, DN-1417, γ -butyrolactone- γ -carbonyl-histidyl-prolinamide citrate, which has less endocrine activity and more central nervous activity, was also observed (Fukuda et al. 1979; Miyamoto et al. 1981; Shikata et al. 1982).

Materials and Methods

Animals used

Male Sprague-Dawley rats weighing 230-275 g were anesthetized with urethane (0.8 g/kg, ip) and α -chloralose (80 mg/kg, ip).

Unit recording

Anesthetized rats were mounted in a Kopf stereotaxic frame with an incisor bar 2.4 mm below the ear bars. The right cerebral hemisphere was exposed and covered with 2% agar dissolved in Tyrode's solution. The recording electrode was lowered through a burr hole in the skull to the appropriate site according to coordinates of König and Klippel (1963). The coordinates used for cerebral cortex, caudate-putamen and nucleus accumbens were 9400 μm -9800 μm anterior, 900 μm -1400 μm lateral to sagittal sinus at various depths.

The extracellular unit recording technique was similar to that described by Oomura (1976). Briefly, micropipettes filled with 0.5M sodium acetate saturated with Pontamine sky blue with tip diameters of less than 1 μm were used (tip impedance: 10-15 M Ω). A single recording electrode was attached with polystyrene Q-DOPE (G.C. Electronics) to a seven barrelled glass micropipettes for drug application.

Substances were applied by passing a constant current of appropriate polarity and strength through the pipette. Since almost all the neurons had a very low spontaneous firing rate, the firing rate was maintained at about 10 spikes/sec by continuous glutamate (1-10 nA) application, so the drug effects could be observed. Only neurons which were excited by glutamate were used in these experiments. The potentials were amplified, and the output from the preamplifier was recorded on an oscilloscope (VC-9, Nihon Kohden) for initial observation, and entered into a window discriminator and rate meter (time

constant: 1 sec). Data was stored on a magnetic tape recorder (R 280 LT, TEAC).

Drugs used

Each barrel was filled with one of the following substances for microelectrophoretic application: 0.5M TRH-T (L-pyroglutamyl-L-histidyl-L-prolinamide L-tartrate monohydrate, Takeda) dissolved in 0.5N NaOH at pH 5.5-6.0; 0.5M DN-1417 (γ -butyrolactone- γ -carbonyl-L-histidyl-L-prolinamide citrate, Takeda) dissolved in 0.5N NaOH at pH 5.0-5.5; 0.5M dopamine HCl (DA, Sigma) at pH 5.0-5.5; 0.5M methamphetamine HCl (MAP, Dainippon) at pH 5.5; 0.5M acetylcholine chloride (ACh, Wako Pure Chemicals) at pH 5.0; 50 mM γ -aminobutyric acid (GABA, Wako Pure Chemicals) dissolved in 0.5M NaCl at pH 6.0-6.5; 0.5M L-glutamate (Wako Pure Chemicals) at pH 7.5; and 0.5M NaCl at pH 6.0-6.5. Haloperidol (Serenace®, Dainippon) diluted with 0.9% NaCl was injected ip to some animals.

Criteria for drug effects

An increase or decrease in firing rate at 30% or more after drug application was considered to be an excitation or inhibition, respectively.

Histological identification of electrode location

At the termination of the experiment, the recording site was marked for histological identification by injecting Pontamine sky blue as an anion with a continuous DC current for 10 to 20 min.

Results

Effects of TRH and DN-1417 on the cerebral cortex, caudate-putamen and nucleus accumbens neurons

As shown in Table 1, 46 of 125 and 46 of 143 cerebral cortical neurons were suppressed by TRH and DN-1417, respectively. The majority (62 and 66%) of the cortical

neurons were unaffected by TRH and DN-1417. An excitatory response was induced by TRH and DN-1417 in less than 2% of the neurons. About one-third of the caudate-putamen neurons were suppressed, two-thirds were unaffected, and less than 3% of the neurons were excited by TRH or DN-1417 application.

85 and 89% of the nucleus accumbens neurons were affected by TRH and DN-1417, respectively. Inhibitory effects were observed in about 73% of the neurons and excitatory responses were observed in 12 and 17% of the neurons during TRH and DN-1417 application, respectively. The proportion of excitatory responses induced by TRH and DN-1417 was greater than in cortical and caudate-putamen neurons.

The effects of TRH and DN-1417 were dose-dependent and reproducible, irrespective of the number of applications. The latency of onset of the drug effect was 2 to 20 sec. TRH and DN-1417 almost always produced the same response in individual neurons.

Effects of DA, MAP, GABA and ACh on activities in neurons of the cerebral cortex, caudate-putamen and nucleus accumbens

DA: Almost all neurons in the cerebral cortex, caudate-putamen and nucleus accumbens were affected by DA application (78, 94% and 96%, respectively). Its primary effect was suppressive (Table 1).

In the nucleus accumbens, the excitatory effect of DA was observed more frequently (9.9%) than in the other two regions. DA produced a dose-dependent effect with an onset latency of 2 to 5 sec (Fig. 1).

The effects of TRH, DN-1417 and MAP on DA-responsive neurons were studied (Fig. 2). It was noted that TRH and DN-1417 had similar actions on the DA response in most of the nucleus accumbens neurons, which responded to DA by either inhibition or excitation. TRH and DN-1417 had smaller inhibitory effects in cortical

TABLE 1

Number of neurons affected by TRH, DN-1417, dopamine, methamphetamine (MAP), acetylcholine (ACh) and GABA

	Number of neurons tested	Excited (%)	Inhibited (%)	Unaffected (%)
Cortical neuron				
TRH	125	1 (0.8)	46 (36.8)	78 (62.4)
DN-1417	143	3 (2.1)	46 (32.2)	94 (65.7)
DA	171	2 (1.2)	131 (76.6)	38 (22.2)
MAP	45	1 (2.2)	33 (73.3)	11 (24.5)
ACh	147	109 (74.1)	27 (18.4)	11 (7.5)
GABA	65	0 (0.0)	65 (100.0)	0 (0.0)
Caudate-putamen neuron				
TRH	97	3 (3.1)	32 (33.0)	62 (63.9)
DN-1417	105	3 (2.9)	27 (25.7)	75 (71.4)
DA	132	3 (2.3)	121 (91.6)	8 (6.1)
MAP	42	0 (0.0)	34 (81.0)	8 (19.0)
ACh	98	88 (89.8)	6 (6.1)	4 (4.1)
GABA	23	0 (0.0)	23 (100.0)	0 (0.0)
Nucleus Accumbens neuron				
TRH	246	30 (12.2)	179 (72.8)	37 (15.0)
DN-1417	239	40 (16.7)	172 (72.0)	27 (11.3)
DA	274	27 (9.9)	236 (86.1)	11 (4.0)
MAP	40	6 (15.0)	29 (72.5)	5 (12.5)
ACh	75	54 (72.0)	14 (18.7)	7 (9.3)
GABA	49	0 (0.0)	49 (100.0)	0 (0.0)

Fig. 1. Dose-dependent effects of electrophoretically applied dopamine (DA), TRH and DN-1417 (DN) on the firing rate of a neuron in the nucleus accumbens. The neuron was driven by the continuous electrophoretic application of glutamic acid (5 nA). The actions of TRH and DN were similar to the actions of DA.

Fig. 2. Effects of TRH, DN-1417 and Methamphetamine on the neurons which were inhibited or excited by dopamine in the neurons of nucleus accumbens (NAC), cerebral cortex (CC) and caudate-putamen (CPU). Figures in the circle indicate the percent of neurons which were inhibited or excited by TRH, DN-1417 and methamphetamine. Number of neurons tested was 10 to 204. (-): neurons inhibited by dopamine, (+): neurons excited by dopamine.

and caudate-putamen neurons which responded to DA than in the nucleus accumbens. MAP produced an effect similar to DA in all three brain regions.

MAP: The effect of MAP on neurons in the cortex, caudate-putamen and nucleus accumbens was predominantly suppressive (73, 81 % and 73 %, respectively). Only one of the 45 cells in the cortex and none of 42 cells in the caudate-putamen, gave an excitatory response to MAP.

In the nucleus accumbens, MAP induced an excitatory response more frequently (15 %) than in the other two regions (Table 1). The latency of onset for the drug effect was 2 to 5 sec.

GABA: All neurons were suppressed by GABA and the effect was dose-dependent. The latency of onset for GABA was shorter than for the other drugs. A postinhibitory excitation, after the GABA application, was frequently observed.

ACh: As shown in Table 1, ACh induced excitatory effects on more than 70 % of the neurons in the cerebral cortex, caudate-putamen and nucleus accumbens. In-

hibitory effects were also seen in the cerebral cortex (18.4 %), caudate-putamen (6.1 %) and nucleus accumbens (18.7 %). The effects of ACh were dose-dependent, and the onset latency for ACh was 2 to 5 sec. A rebound inhibition after a pronounced excitation was observed in some neurons.

Effect of haloperidol on the effects of TRH, DN-1417 and DA in the nucleus accumbens

Haloperidol, ip, slightly increased the spontaneous firing rate of the nucleus accumbens neurons in which DA had an inhibitory action (Fig. 3), and it decreased the spontaneous rate if DA had an excitatory effect. The effect of haloperidol pretreatment was studied on the neurons which responded to DA, TRH and DN-1417 with either inhibition or excitation. The inhibitory action of DA, TRH and DN-1417 were markedly attenuated by pretreatment with haloperidol. The excitatory effects of DA, TRH and DN-1417 were also attenuated by haloperidol (Fig. 3).

Fig. 3. Effect of haloperidol (HAL; 2 and 1 mg/kg, ip) on the inhibitory and excitatory actions of electrophoretically applied TRH, dopamine (DA) and DN-1417 (DN). The neuron was driven by the continuous application of glutamic acid (15 nA). After the HAL injection, the inhibitory and excitatory actions of TRH, DA and DN were almost completely blocked.

Discussion

Microelectroretic applications of TRH and DN-1417 affected a large proportion (85–89 %) of neurons in the nucleus accumbens, but only a small proportion (less than 40 %) of neurons in the cerebral cortex and caudate-putamen. DA affected almost all neurons in these regions (78–96 %). There are several reports on the effects of TRH on cortical neurons which describe suppressive effects (Morley, 1979; Renaud and Martin, 1975), no obvious effects (Winokur and Beckman, 1978; Yarbrough, 1976) and either excitatory or inhibitory effects (Braitman et al. 1980).

TRH and DN-1417 suppressed the firing in 37 and 32 % of the cortical neurons, respectively. Bunny et al. (1976) reported that DA and norepinephrine elicited an inhibitory action on neurons in layers II, III, V and VI of the frontal cortex. Stone et al. (1975) found that DA and amphetamine

had an inhibitory action on almost all cortical neurons. TRH and DN-1417 have been reported to have a stimulatory effect on [14 C]-norepinephrine release from cortical slices although they are less active than MAP (Narumi et al. 1979). The results of the present study suggest that the effect of TRH or DN-1417 on cerebral cortical neurons is mediated via a catecholaminergic system in the brain.

Yarbrough (1976) and Braitman (1980) reported that TRH potentiated the excitatory action of ACh on cortical neurons. In other reports, no potentiating effect of TRH on ACh-responsive cortical neurons was found (Renaud and Martin, 1975). In the present study, TRH or DN-1417 affected some ACh-sensitive and ACh-insensitive neurons in the cerebral cortex. This was also observed in the caudate-putamen and the nucleus accumbens neurons. Moreover, GABA did not act like TRH, DN-1417 and DA in regard to latency,

duration and direction of the GABA effect. This was also found in the caudate-putamen and the nucleus accumbens neurons.

In caudate-putamen which is the terminus of the nigrostriatal DA system, TRH and DN-1417 affected 36 and 28.6 % of the neurons mainly in an inhibitory manner. On the other hand, DA and MAP inhibited most all the neurons (92 and 81 %). TRH and DN-1417 had the same effect on caudate-putamen neurons as DA in 37 and 28 % of the neurons tested, respectively. MAP produced the same effect as DA in 86 % of the caudate-putamen neurons. There are contrasting reports (Connor, 1970; Kitai et al. 1976; McLennan and York, 1967; Spencer and Havlicek, 1975) whether DA can produce an excitatory or inhibitory action on the caudate-putamen neurons, but the reason for this discrepancy is unclear (Woodruff et al. 1976).

It has been proposed that the nucleus accumbens is a functional interface between the limbic and motor systems, and that DA has a role in modulating the nucleus accumbens (Mogenson et al. 1980; Yim and Mogenson, 1982). TRH or DN-1417 applied microelectrophoretically affected most neurons in the nucleus accumbens (85 % and 89 %, respectively), mainly in an inhibitory manner. However, excitatory effects were also detected with TRH and DN-1417 application in 12 and 17 % of the neurons, respectively. DA also had excitatory and inhibitory effects on the nucleus accumbens neurons in the present investigation.

Both the excitatory and inhibitory effects of DA were reduced by pretreatment with haloperidol, a DA receptor antagonist. Almost all cells responding to DA also responded to TRH, DN-1417 or MAP in a similar-manner. Furthermore, both the excitatory and inhibitory effects of TRH and DN-1417 in the nucleus accumbens neurons were attenuated or blocked by haloperidol treatment. These results sug-

gest that the action of TRH or DN-1417 on the nucleus accumbens neurons is mediated via either a direct activation on DA receptors or an indirect activation of an endogenous dopaminergic system within the nucleus accumbens.

Miyamoto and Nagawa (1977) reported that the mesolimbic dopaminergic system was involved in the motor stimulatory action of TRH. An ip injection of TRH, or a bilateral microinjection of TRH into the nucleus accumbens, induced a motor stimulatory action in rats. This action was attenuated by pretreatment with ip or bilateral injection of haloperidol into the nucleus accumbens, and by systemic administration of pimozide (a DA receptor antagonist), or α -methyl-p-tyrosine (a tyrosine hydroxylase inhibitor), and was augmented by pargyline (a monoamine oxidase inhibitor). Also, there is evidence that TRH increases [^3H]-DA release from the rat nucleus accumbens slices *in vitro* (Kerwin and Pycock, 1979; Miyamoto et al. 1979). These findings indicate that the effects of TRH and DN-1417 on the nucleus accumbens neurons are mediated via the dopaminergic system in the nucleus accumbens. A large dose of TRH (100 mg/kg, ip) is required to produce a rotating behavior directed to the lesioned side in rats with a unilateral nigrostriatal lesion from the administration of 6-hydroxydopamine (Fukuda et al. 1979). In neurochemical studies, higher concentrations of TRH are necessary to release [^3H]-DA from striatal slices than from nucleus accumbens slices *in vitro* (Narumi et al. 1983). In contrast to the effect of TRH, no differences were found in the concentrations of MAP necessary to release [^3H]-DA in nucleus accumbens and striatal slice preparations (Miyamoto et al. 1979; Narumi et al. 1979). These findings agree with the present data that TRH and DN-1417 act more selectively on the nucleus accumbens neurons than on the cortical and caudate-putamen neurons.

In summary, more cells which were sensitive to TRH and DN-1417 were found in the nucleus accumbens than in the cortical and caudate-putamen. Also, the effect of TRH and DN-1417 on the nucleus accumbens neurons is probably mediated via a dopaminergic system, which releases DA within the nucleus accumbens. Moreover, the present study supports the hypothesis that the nucleus accumbens has a role in eliciting the locomotor stimulatory action of TRH and DN-1417. Since it has been proposed that the nucleus accumbens is a functional interface between the limbic and motor systems, further experiments should be undertaken to clarify the physiological role of TRH in the nucleus accumbens.

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