Atropine-Induced Changes of Cerebral Dopamine Turnover

Systemic administration of atropine has been shown to reduce the turnover of dopamine (DA) in the basal ganglia. The drug decreases the content of homovanillic acid (HVA) in the striatum without affecting the dopamine concentration[1,2] and it delays the disappearance of endogenous cerebral DA induced by α-methyl-*p*-tyrosine[3]. In addition, atropine counteracts the HVA rise in the brain caused by neuroleptics[1,3].

In the present paper, the action of atropine has been further analyzed by comparing the turnover of cerebral DA after administration of the drug into the peritoneal cavity or into the cerebral ventricles.

Experimental. Male albino rats of Wistar origin (Füllinsdorf) weighing 300–400 g received various doses of atropine either i.p. or into the right lateral ventricle of the brain through a permanent cannula implanted 1 – 2 weeks before[4]. The animals were killed by decapitation at various time intervals after administration of the drug. Rats injected with saline served as controls. In brain (without cerebellum and medulla oblongata) HVA[5] (with some modifications[6]), DA[7], and 5-hydroxyindolacetic acid[8] were determined.

Results and discussion. As shown before[1,2] i.p. injection of atropine causes in the brain of rats a significant decrease of endogenous HVA without changing the DA content. 5 mg/kg atropine diminish the HVA level to about 60% of the control values, but a further increase of the dose (up to 40 mg/kg) has no significant additional effect (Figure 1).

Administration of atropine into the cerebral ventricles causes a pronounced rise of HVA in the whole brain without affecting the DA concentration. Similar results were obtained when the striatum was analyzed instead of the whole brain. Doses of atropine as low as 50 μg have already a significant effect and with 200 μg the HVA level rises to about 200% as compared to controls (100%). The maximal effect of 200 μg atropine is reached after 1 h (Figure 2). The content of cerebral 5-hydroxyindolacetic acid is at the best slightly increased after atropine given either i.p. (5–40 mg/kg) or into the cerebral ventricles (200 μg) (Table). Therefore, the turnover of 5-hydroxytryptamine does not seem to be affected to a major extent by atropine. These experiments indicate that atropine acts differently on cerebral DA according to the route of administration. Thus, i.p. injection of the drug probably diminishes whereas intraventricular administration seems to enhance the turnover of brain DA. An inhibition by intraventricular atropine of the outflow of HVA from the brain into the blood is unlikely as shown by experiments with the benzoquinolizine derivative Ro 4–1284[9]. This drug, due to a rapid liberation of endogenous DA in the brain, causes a marked rise of cerebral HVA. This increase is further enhanced by probenecid, a known inhibitor of the transport of the phenolcarboxylic acids from the brain, but not by atropine[6]. In addition, the effect of intraventricularly administered atropine is probably not due to a blockade of the DA reuptake into the striatal synapses, or to a local anesthetic action. In fact, injection of atropine (100 μg) into the striatum does not affect the levels of both DA and HVA in this structure and intraventricular administration of procaine (200 μg) has no influence on the cerebral HVA content[6].

The reason for the opposite action of atropine depending on its site of injection remains to be investigated. The effect of the drug administered i.p. does not seem to be of peripheral origin, since methylscopolamine, an anti-

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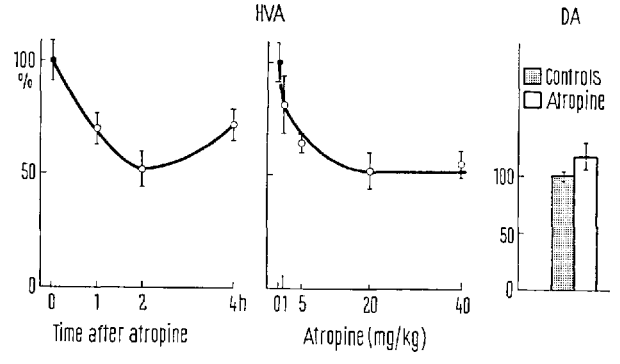

Fig. 1. Effect of the i.p. injection of atropine on the content of endogenous homovanillic acid (HVA) and dopamine (DA) of the rat brain. HVA was measured at various time intervals after administration of 20 mg/kg atropine (left) or 2 h after varying doses of the drug (middle). DA was determined 2 h after 40 mg/kg atropine (right). The values are expressed in % of controls (= 0.093 ± 0.006 μg/g for HVA: point 0 on the abscissa; 0.75 ± 0.02 μg/g for DA). Averages with SE of 2–5 duplicate experiments each with 2 pooled brains. All the values of HVA after atropine are significantly different from controls ($p < 0.01$) with the exception of that obtained with 1 mg/kg of the drug. The values of DA in control and treated animals are not significantly different from each other ($p > 0.05$).

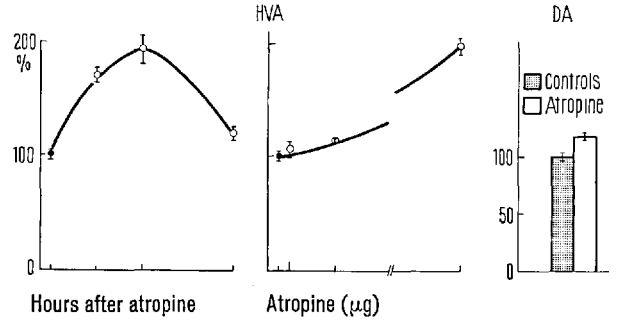

Fig. 2. Effect of intraventricular administration of atropine on the levels of endogenous homovanillic acid (HVA) and dopamine (DA) in the rat brain. Atropine was injected into the right lateral ventricle of the brain. The animals were sacrificed at various time intervals after 200 μg (left) or 1 h after varying doses (middle) of the drug, respectively. DA was measured 1 h after 200 μg atropine (right). The values are expressed in % of controls (= 0.076 ± 0.004 μg/g for HVA: point 0 on the abscissa; 0.81 ± 0.03 μg/g for DA) and represent averages with SE of 2–5 duplicate experiments each with a pool of 2 brains. Only the value of HVA obtained after 10 μg atropine is not different from controls ($p > 0.05$). All the other values are significantly different from controls ($p < 0.01$).

cholinergic agent which does not penetrate into the brain, has no effect on the cerebral DA turnover[3]. As a working hypothesis, it may be assumed that two cholinergic systems are involved which influence the regulation of the cerebral DA turnover in an opposite manner. This might be the reason why the cerebral HVA decreases only to 60% even after high i.p. doses of atropine. The dependence of the effect of atropine on the route of administration is possibly explained by differences in the distribution of the drug in the brain. After intraperitoneal injection the distribution of atropine might be such that the stimulatory system is preferentially inhibited whereas on intraventricular administration the drug may mainly interfere with the inhibitory projection.

The cerebral localization of the two cholinergic systems is not known. Preliminary experiments indicate that the inhibitory system may influence the dopaminergic cell bodies of the substantia nigra. Thus, supranigral injection of atropine causes a marked increase of the striatal HVA without changing the DA concentration[6].

Effect of i.p. or intraventricular administration of atropine on the level of the cerebral endogenous 5-hydroxyindolacetic acid in rats

Time	Atropine			
(h)	Intraperitoneal (mg/kg)			Intraventricular (µg)
	5	20	40	200
1/2				112.4 ± 2.3
1		100.7 ± 0.8		118.1 ± 4.2
2	115.4 ± 4.7	101.6 ± 6.5	121.9 ± 4.4	110.9 ± 3.5
4		94.0 ± 0.5		

The values are expressed in % of saline injected controls (0.40 ± 0.01 µg/g) and represent averages with SE of 2–5 duplicate experiments each with 2 pooled brains.

Zusammenfassung. Nach Applikation von Atropin in die Hirnventrikel von Ratten kommt es zu einer starken Erhöhung der Homovanillinsäure (HVA) im Gehirn, während dessen Gehalt an Dopamin nicht vermindert wird. Intraperitoneale Injektion von Atropin bewirkt dagegen eine Abnahme von HVA, ebenfalls ohne Beeinflussung des Dopamins im Gehirn. Es wird vermutet, dass zwei regulatorische cholinergische Mechanismen bestehen, die eine entgegengesetzte Wirkung auf den Dopaminumsatz der basalen Ganglien haben.

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[9] 2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo [*a*] quinolizine.

Der Einfluss von adrenergen Rezeptoren-Blockern auf die Wirksamkeit von Strahlenschutzsubstanzen

Zur Deutung der Wirkung von Strahlenschutzsubstanzen wird von uns angenommen[1], dass zum mindesten in einer Anzahl von Fällen eine enge Beziehung der Schutzsubstanz zu dem cAMP-Mechanismus[2] besteht. Um die Richtigkeit unserer Annahme zu prüfen, wurde von uns die Frage untersucht, ob durch eine Blockade von adrenergen Rezeptoren die Wirksamkeit bestimmter Strahlenschutzsubstanzen beeinflusst wird. Bei den zu diesem Zwecke durchgeführten Versuchen sind wir in der Weise vorgegangen, dass wir Mäuse (25 g K.-Gew.) 15 Min. vor der Injektion der jeweils verwendeten Schutzsubstanz entweder 0.5 mg/Maus Phentolamin (Regitin), 0,25 mg/Maus Propranolol (Dociton) oder 0,5 mg/Maus LB 46 (Visken) i. p. applizierten. Die Schutzsubstanzen, die wir entweder i.p. oder s.c. verabreichten, waren: S,β-Aminoäthylisothiuronium (AET, 6,0 mg/Maus), Cystamin (6,0 mg/Maus), 5-Hydroxytryptamin (Serotonin, 1,0 mg/Maus), Trianisyl-2-Chloräthylen (TACE, 1.0 mg/Maus) oder das Lipopolysaccharid (LPS) von *E. coli* (10 µg/Maus). Gelöst wurden die Substanzen entweder in Aqua dest. (AET, Cystamin, Serotonin, LPS) oder in Olivenöl (TACE). Die Bestrahlung der Tiere mit Röntgenstrahlen (150 kV, 20 mA, HWS: 0.87 mm Cu, 85 R/min) erfolgte je nach der Art der verabreichten Schutzsubstanz zu verschiedenen Zeitpunkten nach deren Injektion (Serotonin: 5 Min., Cystamin 15 Min., LPS: 24 h und TACE: 10 Tage). Die applizierte Strahlendosis betrug bei der Prüfung des Einflusses verschiedener Rezeptoren-Hemmer auf die Wirksamkeit des LPS 750 R.

Bei einem 2. Versuch, bei dem die Wirkung des β-adrenergen Rezeptoren-Blockers LB 46 (Visken) in Zusammenhang mit den verschiedenen verwendeten Schutzsubstanzen untersucht wurde, bestrahlten wir die Versuchstiere mit Strahlendosen im Bereich zwischen 810 und

Tabelle I. Die Wirkung verschiedener Rezeptoren-Hemmer bei Verabreichung von LPS von *E. coli* als Schutzsubstanz an weibliche Mäuse

Substanz	Rezeptoren-Hemmer	Strahlendosis R	Überlebende Tiere ohne Rez.-Block. (%)	Überlebende Tiere mit Rez.-Block. (%)	*P*
LPS	–	750	89.0	–	
	Phentolamin (Regitin)			57.2	
	Propranolol (Dociton)			58.0	<0.01
	LB 46 (Visken)			64.0	

Überlebensrate von unbehandelten, mit 750 R bestrahlten Tieren nach 30 Tagen: 21,0%.