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An Ethological Analysis of the Effects of Tifluadom on Social Encounters in Male Albino Mice

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BRAIN, P. F., R. SMOOTHY AND D. BENTON. *An ethological analysis of the effects of tifluadom on social encounters in male albino mice.* PHARMACOL BIOCHEM BEHAV 23(6) 979–985, 1985.–The effects of treatment with saline, 0.5 or 1.0 mg/kg of tifluadom were assessed 30 min after injection on the behaviors shown by isolated Alderly Park strain mice in their home cages in the presence of an anosmic 'standard opponent' mouse. Tests involved videotaping encounters and examining the incidences of 45 behavioral elements and their sequences (by producing 'dendrograms'). The kappa agonist appeared to stimulate olfactory exploration of the substrate at the expense of other forms of non-social exploration; it suppressed olfactory investigation of the 'standard opponent'; reduced some aggressive elements and increased immobility (at reportedly non-sedative doses) and fearful activity. The 'dendrograms' revealed that tifluadom greatly altered the relationships between some elements. The higher dose of the kappa agonist resulted in self-grooming and digging (displacement?) being associated with the agonistic items suggesting that these animals evidenced increased timidity in social encounters.

Ethological analysis Kappa agonist Mice 'Standard opponents' Tifluadom

DRUGS influence behavior in complex ways: one of the reasons for this complexity is that behavior itself is an intricate pattern of many postures and responses. The use of videotape recording techniques and computer analysis facilitates the routine use of ethologically-inspired methodologies in the assessment of putative psychoactive drugs. Often the effect of a compound on the patterning of behavior is greater than its action on the quantities of particular elements. A technique has been developed [10] enabling one to perform a sequential analysis of the postures employed in a 'standard opponent' test [6] using laboratory mice. The resulting associations between elements that immediately precede or follow each other are expressed as 'dendrograms' (see later) and preliminary studies with these constructs [3, 7, 8] suggest that they have considerable descriptive power in assessing the subtle behavioral actions of putative anti-aggressive agents (e.g., Duphar's Fluprazine) and antagonists of the opiate/opioid system (naloxone and ICI 154,129).

This present study attempted to further assess the utility of sequence analysis using tifluadom (a benzodiazepine derivative which, although lacking typical minor tranquilizer actions, functions as a kappa agonist producing naloxone-reversible analgesia [15,16]).

METHOD

Male Alderly Park strain mice were used in these studies. They were bred and housed under highly controlled conditions (an ambient temperature of 18–21°C and a reversed lighting schedule with white lights on between 22:30 and 10:30 hr) in the Animal Facility of the University College of Swansea from a stock obtained from I.C.I. Ltd, Alderley Park, Macclesfield, Cheshire. Subjects were weaned at 19–23 days of age and placed into single sex groups of 6 until between 44 and 55 days of age, in opaque cages measuring 30×12×11 cm with a sawdust substrate. Food (Pilsbury's Breeding diet) and water were available ad lib except at the time of behavioral testing. Experimental subjects were individually housed for 21 days before drug treatment and behavioral testing. 'Standard opponent' counterparts [8] were comparably-aged mice that remained in their original groups until testing. Such mice were rendered temporarily anosmic by applying 25 μl of a 4% zinc sulphate solution to their nasal tract whilst they were anaesthetized with ether, both three and one days before the social encounters. Mice treated in this way (used once only) are consistently docile and spend little time in social investigation, thus, when paired with mice which have an intact olfactory system, the latter animals will initiate most of the social encounters and show all the threat and attack.

Thirty minutes before paired encounters in their home cages, the individually-housed mice were given a single subcutaneous injection with one of the following solutions: (1) physiological saline (0.9% saline); (2) 0.5 mg/kg of tifluadom (Sandoz, Switzerland); (3) 1.0 mg/kg of tifluadom.

There were 9–10 subjects in each treatment category. Testing commenced one hour after the start of the dark phase of the illumination cycle and continued for no longer than 3 hr after that time in order to minimize the influence of the known circadian variation in production of endorphins. The doses and time scales selected followed open field studies suggesting that they produced behavioral effects without obvious sedation [5].

TABLE 1

INCIDENCES OF RECORDED INDIVIDUAL POSTURES (MEDIANS WITH RANGES) FOR MICE TREATED WITH DIFFERENT DOSES OF TIFLUADOM

Code	Full-Name of Posture	Saline Control	0.5 mg/kg Tifluadom	1.0 mg/kg Tifluadom
AB	Abbreviated groom	3 (0–9)	2 (0–6)	3 (1–7)
AG	Aggressive groom	1.5 (0–8)	0 (0–6)	1 (0–10)
AK	Attack	3.5 (0–14)	0* (0–2)	0 (0–16)
AP	Approach	46.5 (41–72)	30 (20–40)	32 (13–44)
AT	Attend	8 (4–16)	9 (6–19)	12 (7–31)
BS	Body sniff	34.5 (20–51)	36 (18–45)	27.5 (11–49)
CG	Cringe	0 (0–1)	1 (0–2)	1 (0–7)
CH	Chase	2.5 (0–7)	0† (0–2)	0.5 (0–8)
CO	Crawl over	33.5 (13–46)	11 (4–39)	16 (6–55)
CR	Cagewall rear	64 (45–86)	46* (23–64)	36† (16–68)
CU	Crawl under	7 (4–21)	8 (2–20)	10 (0–18)
DI	Dig	8.5 (0–27)	2 (0–9)	8 (0–16)
EV	Evade	2 (0–6)	3 (0–6)	4 (2–15)
EX	Explore	18 (5–33)	26* (18–35)	33† (19–57)
FD	Fend	0 (0–3)	0 (0–5)	0 (0–13)
FL	Flee	1 (0–4)	2 (0–7)	4* (1–14)
FO	Follow	19 (14–31)	6† (2–22)	10.5† (2–28)
GG	Genital groom	0 (0–1)	0 (0–1)	0 (0–2)
GM	Groom	4.5 (1–10)	1 (0–10)	0 (0–9)
GS	Gential sniff	40 (29–52)	17† (5–43)	25† (8–41)
HG	Head groom	5.5 (1–12)	1 (0–9)	0.5 (0–17)
JU	Jump	0.5 (0–7)	0 (0–0)	0 (0–1)
KD	Kick dig	1 (0–5)	0 (0–3)	0 (0–4)
LU	Lunge	18.5 (0–57)	2 (0–30)	0.5 (0–52)
LV	Leave	35.5 (28–54)	21 (11–29)	13 (7–44)
MT	Mount	0 (0–2)	0 (0–1)	0 (0–1)
NS	Nose sniff	22 (11–39)	18 (10–32)	7.5† (2–29)
PD	Push dig	2 (0–10)	0 (0–25)	0 (0–10)
RE	Rear	18.5 (9–42)	15 (7–38)	11 (0–40)
RT	Retract	12 (6–20)	10 (2–15)	12.5 (6–23)
SA	Stretched attention	1 (0–3)	1 (0–6)	2* (1–13)
SC	Scratch	0.5 (0–2)	0 (0–3)	0 (0–0)
SG	Self groom	0.5 (0–7)	0 (0–6)	1 (0–3)
SH	Shake	2 (0–4)	1 (0–4)	1.5 (0–3)
SO	Sideways Offensive	24.5 (0–70)	1 (0–37)	1 (0–26)
SQ	Squat	1 (0–4)	10‡ (1–19)	14‡ (6–37)
TR	Tail rattle	0 (0–4)	0 (0–1)	0 (0–30)
UO	Upright offensive	6.5 (0–23)	0 (0–7)	0 (0–44)
WA	Wash	2.5 (0–10)	0 (0–8)	1 (0–3)
WK	Walk	65 (51–110)	62 (37–110)	44* (18–108)
WR	Walk round	33 (19–50)	14‡ (6–25)	13‡ (3–42)

*Differs from saline controls $p<0.05$ 2 tailed Mann Whitney 'U' test.

†Differs from saline controls $p<0.02$ 2 tailed Mann Whitney 'U' test.

‡Differs from saline controls $p<0.002$ 2 tailed Mann Whitney 'U' test.

At the time of behavioral testing, a non-injected 'standard opponent' was introduced into the test animal's cage. The wire lid was replaced by a perforated, transparent perspex cover and the encounter was video-recorded from directly above for 10 min. The resulting videotapes had a superimposed time trace and they were initially analysed in terms of the times allocated to broad categories of behavior [5]. Subsequently, the sequences of behavioral elements were obtained using slow motion and frame advance facilities on the recorder. A convention of naming elements was employed that followed the detailed considerations of a number of workers in this laboratory [10].

The method initially enabled one to 'count' the numbers of particular elements occurring in the social interactions. The sequence analysis used to generate 'dendrograms' is complex. Briefly, the videotaped records of the encounters were verbally transcribed on to a tape recorder as a sequence of the resident's postures and movements using a check list of some 41 elements. The order in which the elements occur is then converted into a numerical form by considering each type of element as a 'first act' and recording the elements immediately following it in the sequence (the 'second acts'). The types of elements following this first act and their frequencies of doing so are presented as a row within a 'transition matrix.' The procedure is repeated treating each element in turn as a first act such that *rows* in the matrix indicate events which follow the first act named at the beginning

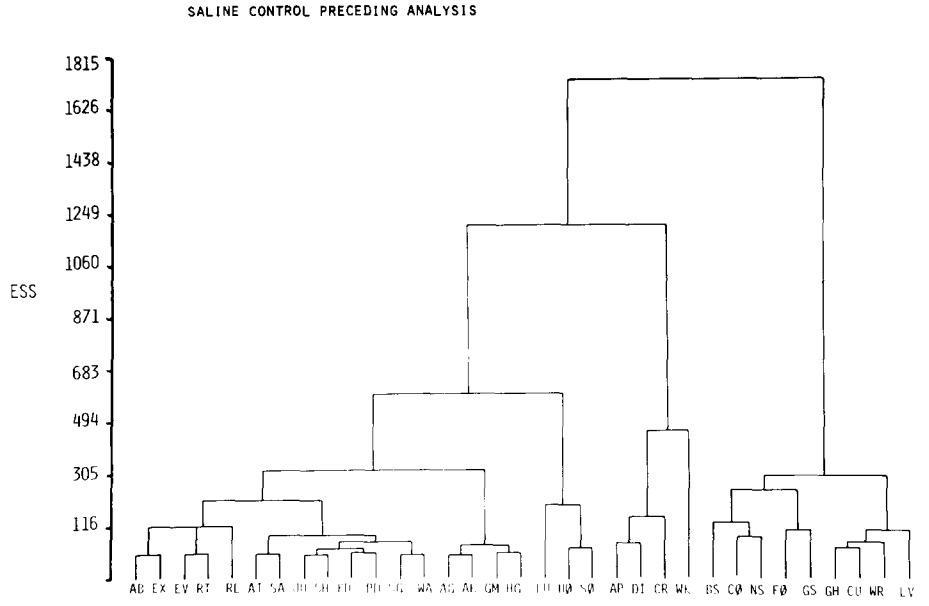

FIG. 1. Saline control preceding analysis.

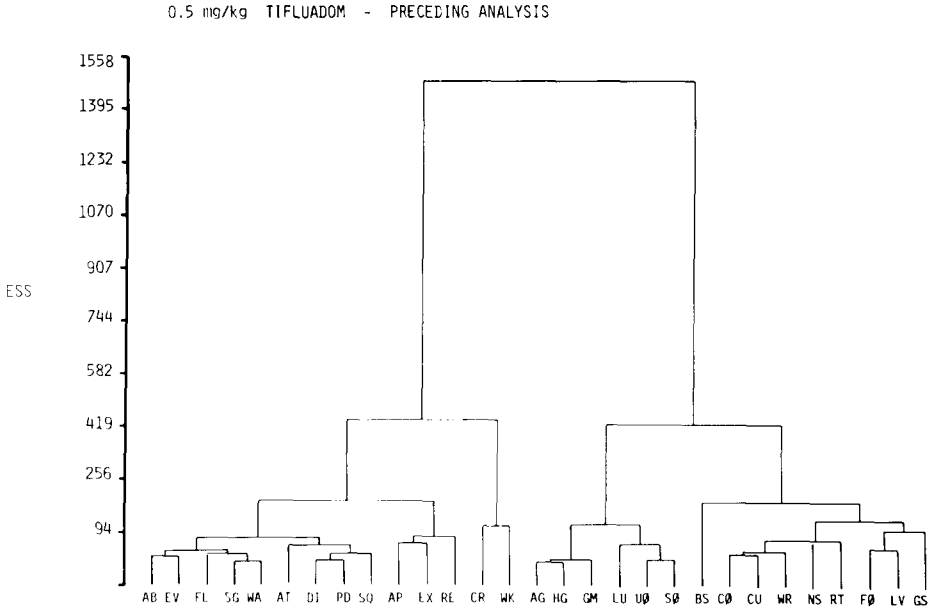

FIG. 2. 0.5 mg/kg Tifluadom—preceding analysis.

of that row and *columns* indicate events which precede the second act at its head. Rows and columns in transition matrices are *not* identical since elements are not generally preceded and followed by the same items. By convention the major (top left to bottom right) diagonal of the matrix is left empty as it is assumed that elements cannot follow themselves. Empty cells create problems in this type of analysis but such effects are minimized by summating matrices for all subjects within a treatment category and applying an arbitrary 'cut-off' value of 5, eliminating cells with a lower combined frequency from the analysis. A positional (based on an element's likelihood of being preceded or followed by the same types of element at comparable frequencies) estimation of element *similarity* was carried out by comparing each column of the transition matrix with every other column using the Chi Square statistic. Each comparison of two columns generates a Chi Square value termed the inter-element 'distance.' The more alike the distribution of elements within the columns, the smaller the 'distance' between these second acts and the greater their positional similarity. Distances are entered into a 'distance matrix' which summarises associations between elements in terms of the events which *precede* them in the sequence. A *following* analysis is performed by comparing rows of the transition matrix. A cluster analysis is then used to search for groups of similar elements. The agglomerative, hierarchical technique (the Error Sum of

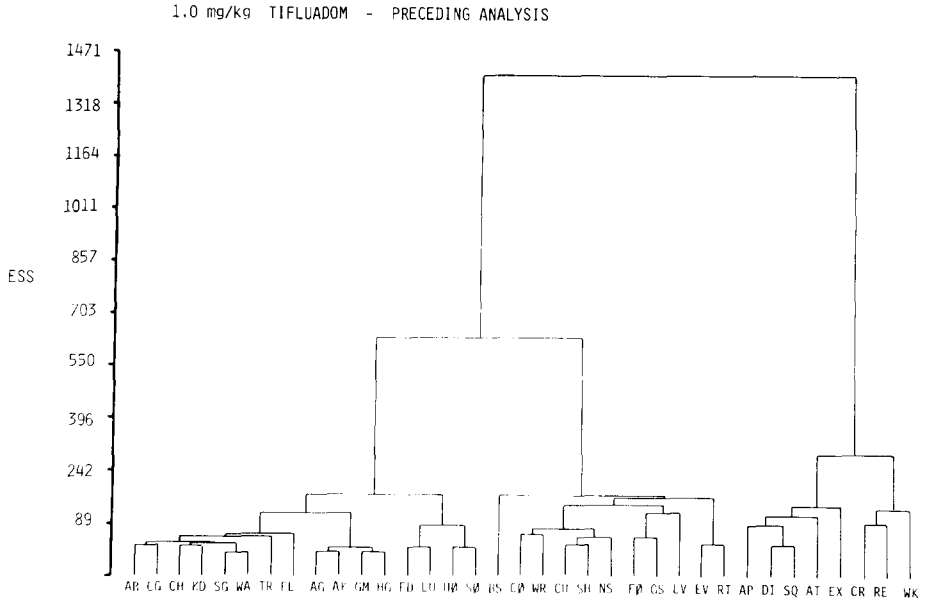

FIG. 3. 1.0 mg/kg Tifluadom—preceding analysis.

Squares Method after Ward) used here fuses elements into successively larger clusters that do not overlap. The fusions of elements are visually represented by a computer-drawn construct called a 'dendrogram.' A 'dendrogram' resembles an inverted tree with the elements showing the highest degree of association being linked nearest the tips of its extremities. The vertical axis values of the figures do not refer to individual clusters but to all groupings formed below that point, i.e., the value is cumulative. When interpreting 'dendrograms,' one should regard clusters formed at lower error sum of squares (ESS) values as being more 'compact' than those formed at higher values. Large increments of ESS produced by fusing two clusters support the contention that their constituent elements are dissimilar, i.e., that the clusters are 'discrete.' The rationale behind the construction of and the interpretation of 'dendrograms' is provided in Jones and Brain [10]. For the sake of brevity (and as no major interpretational differences were evident when using both in this particular study) only *preceding* 'dendrograms' are presented here. All the figures used here were considered at an ESS around 700 to obtain *clusters* of elements (a, b or c) and then around 250 to identify *sub-clusters* (a1, a2, a3, b1, etc.).

RESULTS

The medians and ranges of the numbers of elements occurring in the different treatment groups are given in Table 1. Mann-Whitney 'U' test comparisons between saline-treated controls and drug-exposed animals are provided where appropriate.

Tifluadom produced a range of significant changes in individual behavioral elements. Interestingly, this drug reduced both 'cagewall rear' and 'walk' but increased 'explore.' Although tifluadom increased 'stretched attention,' it markedly reduced 'follow,' 'genital sniff' and 'nose sniff.' Small but significant suppressions of 'attack' and 'chase' were produced by the lower dose of this drug. There was a marked increase in 'squat,' an immobile posture, and a significant augmentation of 'flee' in animals receiving tifluadom.

The 'dendrogram' for preceding elements in saline-treated animals is given as Fig. 1. This reveals three clusters consisting of a number of sub-clusters, namely: 'a'. a wide range of tentative exploratory, allogrooming and attack-related elements (AB-SO); 'b'. a discrete set of non-social exploratory activities (AP-WK); 'c'. some persistent social investigatory actions (BS-LV).

Cluster 'a' may be regarded as consisting of three sub-clusters: a1. tentative exploration, digging and care of body surface (AB-WA); a2. grooming plus attack (AG-HG); a3. attack and threat (LU-SO).

Cluster 'b' has AP, DI and CR sub-clustered (b1) but WK (b2) is on its own.

Cluster 'c' also contains three sub-clusters: c1 and c2. concerned with olfactory investigation of the 'standard opponent' (BS-NS and FO-GS); c3. persistent physical contact with that animal (CH-LV).

The 'dendrogram' for mice treated with 0.5 mg/kg of tifluadom is given as Fig. 2. It consists of only two clusters, namely: 'a'. a group of non-social exploratory elements with digging, approach and some tentative and defensive activity (AB-WK); 'b'. social investigatory behavior with threat and attack (AG-GS).

Cluster 'a' consists of two sub-clusters: a1. non-social exploration with digging, approach and some tentative and defensive activity (AB-RE); a2. ambulatory non-social exploration (CR-WK).

Cluster 'b' also consists of two sub-clusters: b1. allogrooming plus threat (AG-SO); b2. olfactory investigation of and physical contact with the 'standard opponent' (BS-GS).

The 'dendrogram' for subjects given 1.0 mg/kg of tifluadom is given as Fig. 3. It also consists of two clusters, namely: 'a'. a very varied grouping of items related to care of body surface, defensive, fearful, threatening, attacking and social investigatory elements (AB-RT); 'b'. non-social exploration plus dig, tentative approach and immobility (AP-WK).

Cluster 'a' consists of two sub-clusters: a1. care of body surface plus threat, defense and attack (AB-SO); a2. olfac-

FIGURE 4

A Synopsis of the Preceding 'Dendrogram'

Structures of Mice Treated with Saline or Tifluadom.

TREATMENT	CLUSTERS		
Saline	a	b	c
	a1 non-social exploration with self-grooming and dig.	b1 approaching, digging and cage-wall rear.	c1 olfactory investigation of 'standard opponent'.
	a2 grooming 'standard opponent' with attack *	b2 walk	c2 olfactory investigation of 'standard opponent.
	a3 attack *		c3 physical contact with above.
0.5 mg/kg Tifluadom	a	b	
	a1 non-social exploration, self-grooming, washing and digging with squat and flee.	b1 grooming 'standard opponent' with threat and attack *	
	a2 non-social exploration	b2 olfactory investigation of and physical contact with 'standard opponent'.	
1.0 mg/kg Tifluadom	a	b	
	a1 non-social exploration with digging and squat.	b1 digging, self-grooming, wash, threat, flee and cringe, grooming 'standard opponent' with threat and agonistic behavior. *	
	a2 non-social exploration.	b2 olfactory investigation of and physical contact with 'standard opponent'.	

* Position of threat and attack-related behaviors.

FIG. 4. A synopsis of the preceding 'dendrogram' structures of mice treated with saline or tifluadom.

tory investigation of and physical contact with the 'standard opponent' with some avoidance of that animal (BS-RT).

Cluster 'b' also contains two sub-clusters: b1. tentative approach plus digging and immobility (AP-EX); b2. ambulatory non-social exploration (CR-WK).

In order to facilitate comparisons between the dendrograms, the clusters and sub-clusters for animals treated with saline or a tifluadom dose are presented in Fig. 4. This technique has been successfully used in a study on morphine glucoronide [9]. Note that the clusters in the mice treated with 1.0 mg/kg of tifluadom are reversed for this purpose (their position is somewhat arbitrary and reversing them makes for an easier comparison with the other groups in this table).

DISCUSSION

The present analysis reveals that the picture obtained when considering broad categories of behavior [5] is more complicated when one considers individual elements. Although Benton *et al.* [5] noted that tifluadom *increased* the time allocated to non-social investigation, the only element significantly increased by this drug was 'explore.' Further, this increase had to more than counteract significant *decreases* in 'cagewall rear' and 'walk'—this suggests that the drug greatly stimulates the animal's olfactory investigation to the substrate. The dendrograms confirm that 'walk' can be classified as a non-social exploratory element. All kappa agonists are powerfully sedative and the reduction in rearing may be taken as evidence of this [17]. The fact remains that many elements are unchanged by these doses of tifluadom so it is unlikely that the sedation is marked or that it accounts for all the behavioral changes. The present methodology at least enables one to check for these alternative explanations.

Benton *et al.* [5] recorded that tifluadom *decreased* the time allocated to social investigatory behavior but while 'fol-

low," 'walk round,' 'genital sniff' and 'nose sniff' show drug-induced reductions, 'stretched attention' (a more tentative activity) was actually increased in frequency. This suggests that the drug reduces aspects of olfactory investigation of and physical contact with the 'standard opponent' but that there is some compensatory increase in tentative attention towards that animal. Although Benton *et al.* [5] found no overall increase in attack after tifluadom injection, the incidence of 'attack' and 'chase' are actually *reduced* in subjects given the lower dose of this drug. The specific kappa agonist U-50488 has also been shown to decrease aggressive behavior in such mice [2]. These findings run counter to the prediction that, as naloxone appears to exert an anti-aggressive effect in this situation (e.g., [1, 11, 12, 13, 14]), one might expect opiate agonists to stimulate such activities. Certainly, there is no evidence that the kappa agonist tifluadom exerts any such action.

Benton *et al.* [5] also recorded that tifluadom produced a transient reduction in timid-defensive behavior. It is interesting that this is achieved against a background of an *overall* increase in 'squat' (a slight impairment of motor activity?) and 'flee' (fearful behavior).

These dendrograms confirm that none of the selected drug doses used here produced a gross disorganization of the behavioral elements.

Summary Fig. 4 shows that tifluadom produces a remarkable reorganization of the clustering elements in the treated subjects compared with saline-treated controls. Indeed, an obvious difference following treatment with this kappa agonist is that only *two* major clusters were evident in the 'dendrograms' of mice treated with this compound compared with the *three* seen in saline-treated controls. Associations of elements concerned with olfactory investigation of and physical contact with the 'standard opponent' are clearly visible in all subjects. These are represented as cluster 'c' in the saline-treated subjects but in the tifluadom-injected mice they are a sub-cluster (b2) which is linked to a grouping largely concerned with grooming, threatening and attacking the 'standard opponent' (sub-cluster b1). One should note that the higher dose of tifluadom resulted in fearful, digging and care of the body surface elements being included here also. In the saline-treated controls, grooming, threatening and attacking the 'standard opponent' are sub-clusters (a2 and a3) and are associated with non-social exploration, self-grooming and digging (a1). It is also interesting to note that, although some non-social exploratory and digging elements are grouped in separate clusters (a1, b1 and b2) in the 'dendrograms' of controls, all non-social exploratory elements in the 'dendrograms' of tifluadom-treated subjects occur in a single cluster (a).

As noted earlier, saline-treated subjects show no significant level of either 'flee' (FL) or 'squat' (SQ), both of which can be regarded as expressions of timidity or sedation. In these preceding analyses, the lower dose of tifluadom resulted in FL and SQ appearing in a non-social exploration related cluster that also included digging and washing. The higher dose of this benzodiazepine derivative resulted in the same picture so far as SQ was concerned but FL was associated with agonistic elements along with digging, self-grooming, washing and some other timidity-related elements ('cringe').

In essence, the drug tifluadom appears to make the animals more fearful in social encounters, reducing expressions of prolonged contact with the 'standard opponent' and consequently somewhat lowering intense attack on such animals. In tifluadom-treated mice, there was a compensatory increase in the olfactory investigation of the substrate (non-social behavior). These findings largely confirm the conclusions of Benton *et al.* [2,5] with respect to the actions of this kappa agonist and U-50488 in male mice. The present detailed analysis, however, emphasizes that the arbitrary grouping together of particular behavioral elements can have its pitfalls as some elements allocated to the same class will increase following drug administration, whereas others will decrease or remain unchanged. Further, the functions served by particular elements can change with the application of particular drugs. All these factors suggest that behavioral sequences should at least be examined prior to the interpretation of particular changes.

It would obviously be of great interest to study a much wider range of opioid agonists and antagonists using the methodologies described here. The indications are, however, that this approach represents a valuable way of analyzing drug effects on behavior.

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